INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

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Evidence Gaps – what does Registry Data offer?

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Goals of the platform

In 2011, the legislator initiated a paradigm shift in the field of pharmaceutical supply in Germany, with far-reaching consequences. The principle, based on the AMNOG, provides that: for new active substances brought on the German market, the pharmaceutical company must prove an additional patient-relevant benefit compared to the available standard of treatment – the appropriate comparative therapy (ACT) – if a higher reimbursement price is sought than for the ACT.

The additional benefit is evaluated and determined by the Federal Joint Committee (Gemeinsamer Bundesausschuss), generally on the basis of proposals from the IQWiG. The pricing is determined largely by the result of this additional benefit assessment. In Germany the price is for the first time negotiated between the National Association of Health insurance Funds and the pharmaceutical company.

The assessment of the additional benefit by the G-BA is the result of expert work based on a law (AMNOG) and on procedural and methodical regulations (e.g. IQWiG methods). The active players on the side of the G-BA and the health insurance funds are classified as scientists, hospital physicians and office-based statutory health insurance physicians, the Medical Service of the Health Funds (Medizinischer Dienst der Krankenkassen, MDK) and employees of the insurance fund administration, but also as patient representatives, however, they act on the basis of their own interests. Value dossiers for new drugs, likewise classified and interest-based, are submitted by the pharmaceutical companies to the G-BA, which serve as the basis for the assessment of the additional benefit.

Because the supply of pharmaceuticals to the population is significantly influenced by the assessment of the additional benefit, it makes sense to provide critical and careful support for the assessment process with a focus on identifying possible faults and counteracting imbalances. The Interdisciplinary Platform on benefit assessment set itself the task of supporting the benefit assessment within a small group of experts with the following objectives:

- Discussing the procedures for the assessment of the additional benefit, including in relation to drug approval,
- Working towards international standards of evidence-based medicine and of health economy being adhered to and applied,
- Determining whether and to what extent actual patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life, are identified and which methodological problems occur during the process,
- Identifying possible undesirable developments, in particular with regard to supplying patients with new active substances,
- Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure.

The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. The Advisory Council considers an interdisciplinary discussion regarding the results of the assessment and the applied benefit assessment methods to be essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new drugs for patients earlier than it was previously the case.

The interdisciplinary platform resulted from the discussion process between clinicians and experts. The mutual desire to pool specialist knowledge in the form of interdisciplinary seminars is supported by an open consortium of sponsors. These include Roche Pharma AG, DAK Gesundheit, Xcenda GmbH and Springer Medizin.

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Beyond the gold standard: What potential carries registry data?

By Dr. Pamela Aidelsburger and Dr. Jürgen Bausch

The practice of proving the efficacy of medical inventions by using randomised controlled trials (RCT) is relatively young. The practice only became the Gold Standard in the 80s of the last century. The basis of such trials is rooted in the past, in a time when medical achievements always originated from individual scientific observations of circumstances and at times even from quite odd (self-)experiments. Just as RCT are an advancement of the trial approaches of the past intended to answer contemporary and societal questions, the trial landscape will keep growing and advancing in order to address new facets of prevalent scientific questions. The comparability of results in a domestic and national context will always be an important part. Just as securing trial funding to gain knowledge about the clinically relevant patient benefits for chronic diseases will be.

Just recently, a remarkable exhibition dedicated to the influence the Italian mannerist Caravaggio had on his successors came to an end at the London National Gallery. The city centre and airports of the British metropolis were abundantly draped in promotional billboards: „Beyond Caravaggio".

The impact of the well-received and widely attended special European exhibition was undeniable: The successors and copycats of Caravaggio have studied and copied the Maestro of dramatic illumination and trailblazer of the Baroque splendidly. However, one would be hard-pressed to find among the many epigones one that would command a reputation of superiority over the Maestro himself.

Pharmacology itself could be seen as a certain analogy to these artistic spheres: In order to prove the efficacy of a new drug compared to a placebo or to another effective comparable therapy, one needs a prospective randomised and controlled blind study (RCT). The current Gold Standard. But there is also a lively study landscape beyond that in the pharmaceutical world – just as in the sphere of Caravaggio's art – with a wide range of result qualities.

However, unlike the acknowledgement enjoyed by the great and undisputed Maestros following the Italian late Renaissance artist such as Rembrandt, Rubens and Velázquez, the acceptance of trial results „Beyond RCT" seems rather meagre.

The questions one must always ask: what trial type can compete with RCT? What's equivalent to RCT? When must trial results from studies with substandard protocols be considered „bunk"? This report of the 5. Seminar of the Interdisciplinary Platform on Benefit Assessment documents the efforts undertaken to broach the question which type of trial could potentially match the standard of RCT. The „exhibition" of this year's spring seminar did not even include study results derived from anecdotal evidence, ob-

servational-, or case-control studies. Just like the curators of the London Caravaggio exhibit have decided to leave the cornucopia of bland image copies and various kitschy impressions in their stores.

What was seriously considered and discussed at the past platform seminar, however, were methods and results of registry studies which could potentially provide valuable contributions and additions to existing RCT trials. Especially when such studies are conducted with proper and sustainable methodologies. And all of this does not even take into account that registry studies can provide answers to questions that cannot be answered by RCT methodologies.

To name just one failed example of the use of registry study data, one should note the circumstance that many institutions across Europe use registries in the treatment of haemophilia, but that they use methodologies which are not comparable to each other across different countries. Despite the successful treatment of patients with recombinant factor substitutions in Europe, it remains in question whether the comparatively high and expensive use of Factor VIII preparations in Germany does indeed reduce adverse incidence rates by reducing haemorrhaging in patients compared to Scandinavian countries.

The results from the German rheumatism registry (Rabbit-Register), on the other hand, show that the benefit- and harm potential of the TNFα-inhibitors available on the market are very similar, which negates the need to pick any one particular special product. The dynamics on the German market do not reflect the results of the respective registry evaluation.

Registries have the potential to close evidence gaps. However, the data gained from registries are of course not available early on enough to actually have an effect on early benefit assessments. The only exception would be different marketing approval timelines across different countries resulting in the availability of usable international data.

Treating practitioners as well as payers have an interest in knowing – evidence-based and under quality of care considerations – which of the high-priced therapies e.g. for multiple sclerosis, hepatitis C or some cancers would provide such an outstanding therapy improvement that they should be categorised as first line therapies. This applies all the more to the emerging biosimilar market, where cost savings potentials are currently not being utilised. „Beyond RCT“ does not at all mean „RCT Light“. Much rather, it represents the attempt to illuminate additional aspects of harm- and benefit potentials, especially in actual care application.

In today's trial registry landscape, long-term funding for many active substances is still amiss, and the acceptance of the results in applied care and in benefit assessments by payers doesn't fare much better. Payers prefer new substances assigned to negatively assessed subgroups not to be prescribed over using the results of a registry study, which could be used to identify clinically relevant advantages to patients with incompatibilities to the standard therapy or when there are no improvements.

After Caravaggio, the Maestro of dramatic illumination, many art epochs followed each with their own strengths and weaknesses. They all had one thing in common though: they all dared to do something new. The art itself became more colourful and daring, but not so much as to forget where it came from and always with references to its predecessor where necessary.

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Application for unproven added benefits: legal and ethical aspects

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The (early) benefit assessment of drugs constitutes a somewhat odd amalgamation of scientific methodology and normative political questions. This includes the question of just which conclusions should be drawn from the fact that a given medicine has not (yet) established its added benefit because no corresponding studies have been conducted so far. The practice of capping the reimbursement for such medicines by tying them to the price of the appropriate comparative therapy has caused many cases of market exits. Generally speaking, there is nothing legally wrong with this practice. However, under the „Nikolaus Doctrine", this may lead to patients having a valid claim for reimbursement against their insurers when the drug is being imported from another country. This illustrates that a methodical rigorism of assessments cannot always be practically maintained.

1. The relationship between normativity and factuality

The (early) benefit assessment of drugs is a complex undertaking, in which methodological and normative questions amalgamate into an issue which can only be untangled with great difficulties. Judicial considerations therefore require an exceptionally elaborate analysis to determine whether therapy decisions are transparently based on the „International Standards of Evidence-based Medicine and the Health Economy" (Paragraph 35a Sec. 1 P. 6 No. 2 SGB V), or if they are rather based in political decisions. This differentiation is vital to determine competences: no scientific institute like the IQWiG can make normative political decisions, and in turn, the subtleties of the assessment procedure could hardly fall within the purview of political committees.

This amalgamation of factuality and normativity is particularly prevalent in therapy decisions which are aligned with the principles of evidence-based medicine (EMB). By now, EBM is firmly integrated into the statutory health insurance law (SHI) – especially in the 5th. book of the German Social Insurance Code and in the code of procedure prescribed by the Federal Joint Committee (G-BA) – which one may well consider a tremendous advancement. However, it is always being suspected of being abused as a tool of surreptitious care rationing. Or to formulate it more tactfully, it is often suspected that EBM-based assessment decisions may from time to time take into consideration issues which are not entirely indifferent to cost. This becomes especially apparent when the early benefit assessment concludes that a new drug has no added benefit, while medical societies and patients – let alone the pharmaceutical companies – think otherwise and assume cost saving motives to be a factor in the assessment procedure.

Even the „inventor" of EBM was aware of this problem. In the now famous essay in which Sackett defined EBM („the

faithful, explicit and reasonable use of the currently best external scientific evidence for decisions of the medical treatment of individual patients. The practice of EBM means the integration of individual clinical expertise with the best-possible external evidence from systematic research"), he already stressed: „Some even fear that EBM will be „hijacked" buy payers and managers in order to reduce therapy costs. This would not only be an abuse of the concept but also a fundamental misunderstanding of the actual financial consequences: practitioners of EBM will identify and apply the most effective procedures to improve the quality of life and extend the lifespan of patients; this could lead to cost increases rather than reductions." (Sackett et al., Evidence based medicine: what it is and what it isn't, BMJ 1996; 312, 71 f.; German translation available on the Internet at http://www.ebm-netzwerk.de/was-ist-ebm/leitartikel-sackett).

Thus, the fact that we not only use EBM to treat individual patients but also to manage our healthcare system („evidence-based healthcare") is therefore neither a matter of course nor unproblematic. This applies also and in particular to the question of if and when a medical innovation has proven its added benefit and what therapy policies are then instituted. Here, common sense will dictate a differentiation of the two constellations:

• An assessment based on EBM will occasionally be able to definitely prove that a given new medical approach does not have any added benefit. The fact that the healthcare system will therefore not include the approach into its catalogue of services, or at least refuse to approve (higher) reimbursements, is technically still a normative political decision. However, generally speaking, this is a rather trivial issue.

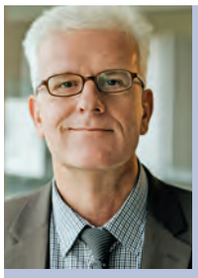
Das Verhältnis von Normativität und Faktizität

- **Wissenschaftlich-methodische vs. normativ-politische Fragen**
  - Unterscheidung schon aus kompetenziellen Gründen wichtig
- **Von der EbM zur evidenzbasierten Gesundheitsversorgung**

„Manche fürchten auch, dass die EBM von Einkäufern von Gesundheitsleistungen und von Managern "gekidnappt" wird, um die Kosten der Krankenversorgung zu reduzieren. Das wäre nicht nur ein Missbrauch des Konzeptes, sondern auch ein fundamentales Missverständnis der finanziellen Konsequenzen: Ärzte, die EBM praktizieren, werden die effektivsten Verfahren identifizieren und anwenden, um die Lebensqualität und -dauer der Patienten zu maximieren; das könnte zu einer Erhöhung statt einer Reduktion der Kosten führen."
(Sackett 1996)

Quelle: Prof. Dr. Stefan Huster

Die Evidenzbasierte Medizin ist immer wieder dem Verdacht ausgesetzt, dass in Bewertungsentscheidungen Überlegungen eingehen, die nicht kostenindifferent sind.



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•If the assessment finds, however, that there is no evidence of an added benefit, the situation changes substantially. The phrasing alone leaves the option that the assessed approach might in fact have the added benefit, and that such benefit will be proven at some future time: simply put, we just don't know of it yet. In this scenario, coming to a normative conclusion becomes much more demanding: Should the approach be included into the service catalogue, and if yes, at what price („money for hope")? To take the position that definitive evidence of the added benefit should be an entrance requirement may make sense, however, it is evidently a political value decision which is neither a matter of course nor justifiable by the knowledge and principles of EBM. In this respect, there is a fluid transition from rationalisation to rationing. Correspondingly, this decision – general or in individual cases – must be made by a committee with a legitimate democratic mandate. Here too, transitional solutions – whatever one may think of them – are conceivable, as demonstrated by the various German legal access requirements for the ambulatory system compared to the hospital system (Para. 135, 137c SGB V), or now also for the „potential"-regulations (see also Para. 137c Sec. 3, Para. 137e Sec. 1 SGB V).

II. The market exit and its causes

1. The unproven added benefit

The aforementioned two constellations can also be found in the early benefit assessment proceedings. Where Para. 5 Sec. 7 No. 5 of the AM-NutzenV speaks of „no additional benefit proven", two quite different case constellations are possible:

• There are meaningful studies which meet the strict requirements of EMB as interpreted by the GBA and IQWiG (particularly RCTs), which factually prove that the assessed drug does not have any added benefit compared to the appropriate comparative therapy (ACT).

• However, it is much more often the case that such studies do not exist. The possible causes are many, ranging from – intentional or negligent – carelessness of the pharmaceutical company to changes to the ACT all the way to no studies being available that meet the required quality standard at the time of marketing authorisation. Especially the – also controversial – tendencies to accelerate the marketing authorisation of drugs („adaptive pathways" or similar) can cause frictions between the marketing authorisation and benefit assessment procedures and the corresponding jurisprudence.

In both scenarios, leaving out reference priced drugs for now, the legal consequences are the same: When the added benefit has not been proven, the price to be negotiated or respectively to be determined by the arbitration board must not exceed the annual therapy costs of the ACT (Para. 130b Sec. 3 SGB V).

2. The decision to leave the market

When the annual cost of the ACT is low, pharmaceutical companies may ask themselves whether they want to make the drug available at all in Germany if the reimbursement price is capped. Since the implementation of the AMNOG procedure, meaning since 2011, there have been already approx. 30 market exits. These were mostly caused by the fact that the respective drugs have not had their added benefit confirmed. In some cases, an added – albeit small – benefit was confirmed, but the pharmaceutical company decided to „opt out" because they considered the price offered by the National Association of the Statutory Health Insurance (GKV-SV) or respectively the price determined by the arbitration board to be unacceptable.

How one should interpret these market exits is not quite clear. One might consider them rather inconsequential, as

Der Marktaustritt und seine Ursachen

- **Die Entscheidung zum Marktaustritt**
  - ca. 30 Marktaustritte seit AMNOG
  - idR. weil kein Zusatznutzen belegt, aber auch denkbar: Zusatznutzen nicht „angemessen" vergütet
  - Unterschiedliche Bewertungen:
    - Kostenträger: rein unternehmerische Entscheidung, für die Versorgung unerheblich
    - Fachges.: Folge unrealistischer Bewertungsverfahren
  - Referenzierungsproblem: Vertraulichkeit der Erstattungsbeträge (§ 130 Ib idF AMVSG-Entwurf)? Trotz „Höhe der tatsächl. Abgabepreise" und Transparenzanforderungen in der GKV?

Quelle: Prof. Dr. Stefan Huster

Die Folgen der Marktaustritte für die Qualität der Versorgung werden von Kostenträgern, Fachgesellschaften und Patienten von Fall zu Fall unterschiedlich beurteilt.

they have no proven added benefit and would therefore not affect therapy quality. This view, which payers prefer, is not always shared by medical societies and patients / the insured. Much rather, these market exits give cause to complain quite frequently – especially in the areas of diabetes and epilepsy therapy and also in oncology. One certain factor to this would be that patients may already be adjusted to a new preparation within the first year after marketing authorisation or while the benefit assessment is still ongoing, or when they have gotten „used" to the drug. However, one should be careful with this argument, because it could mean that immediate access to drugs with new issued marketing authorisations could be prevented by a „fourth hurdle".

One rather serious concern, however, is that the strict requirements placed on the evidence of added benefit may lead to certain drugs that have already been considered proven by practitioners and patients even though their efficacy has not (yet) been sufficiently proven in studies being „left behind".

It is well established that the decision of the pharmaceutical companies is substantially influenced by the fact that Germany is considered a reference market for the price determination in other countries. The legislature has attempted to alleviate fears of a downward spiral being triggered by keeping the reimbursement prices secret. This is not only a bit curious due to the fact that in Germany even the „actual distribution price for other European countries" must be disclosed (Para. 130b Sec. 1 P. 9, Sec. 4 P. 2 SGB V); much rather, this confidentiality also runs afoul of the transparency requirements of a self-administering social insurance system, in which participants want to know which price thesick funds– including in comparison to the reimbursements for other services and drugs – have offered if they want to legitimise its organs by way of ballot elections. It is therefore welcome that these aspirations did not eventually make it into the respective healthcare improvement act (AMVSG).

3. The consequences of the assessments which cause market exits

At any rate, the potentially increasing number of drugs exiting the German market raises new questions. One might wonder what this may mean for the „pharmaceutical location Germany". It also remains to be determined if and how the strict requirements on the benefit assessment in conjunction with the aforementioned pricing consequences will affect the R&D activities of the pharmaceutical companies, and therefore future patient care in general.

However, hereinafter we shall only address the legal consequences of market exits. One may state right from the start: According to not uncontroversial but now esta-

blished legal precedent, pharmaceutical companies do not have a constitutionally protected right to demand that collective insurance systems – in Germany the SHI – procure their products for a price acceptable to them, whatever acceptable may mean. Thus, a complete eschewal of innovative drugs would therefore be sub specie of the basic rights of the pharmaceutical companies a constitutionally sound ascertainment of the SHI service catalogue. Generally speaking, there is really no other way, as the community must be capable of considering how much is to be spent on healthcare. The legally guaranteed privileges of pharmaceutical companies are therefore limited to the non-capricious participation in the collective healthcare system (whereby the drug price regulations not only encompass that statutory carriers but also private health insurers). When the benefit assessment determination resulted in a „no proven added benefit" rating in compliance with the respective statutory regulations, the pharmaceutical company will have no legal recourse against the resulting consequences on pricing regulations: they have then a choice to either exit the market or to accept the (lower) price.

The case might be different for the insured / patients, for whom a market exit initially means that the drug will no longer be available to them. The following elaborations concern their legal position, which has the potential to raise substantial ethical questions when there is an urgent need for care.

III. Benefit entitlements of patients in the event of market exits

1. The requirements set forth by the 5th. book of the social code

In 2015, the Federal Constitutional Court has clarified that those insured by the statutory health insurance are „entitled to a constitutional legislation and to an interpretation of the entitlement laws applicable to the statutory health insurance in keeping with the basic law (...). Particularly in need of legal formulation are the generally permissible (...) methods for the assessment of diagnostic and therapeutic benefit as well as the medical necessity and economic feasibility of new diagnostic and treatment methods. If a service required to treat an illness would be withheld by way of an approval process which does not meet constitutional requirements, the fundamental rights of the insured would have been violated." (FCC on 11/10/2015 1 BvR 2056/12, Rn. 20).

For the benefit assessment – which will have to be revisited – the entire affair is a bit more entangled, because here the result is not an exclusion of a service but a price determination, whereby the opt-out decision is ultimately made by the pharmaceutical company. However, one would generally have to say that the insured could have had their rights violated if the institutions involved in the assessment – meaning IQWiG and particularly the GBA – did not comply with statutory requirements.

This raises the question of whether the strict requirements placed on assessment and studies by IQWiG and the GBA are in fact legal. However, from a legal point of view, this immediately poses a problem because the law does not provide substantial instructions beyond the previously mentioned reference to the „international standards of evidence-based medicine and the health economy". The so-called AM-NutzenV ordinance fails to answer the question of just when studies of the highest evidence level can be demanded in the course of establishing the evidence of the added benefit. Para. 5 Sec. 3 P. 5 of AM-NutzenV merely states: „Where it is impossible or inappropriate to conduct or demand studies of the highest evidence level, evidence of the next-best evidence level must be submitted."

This prescriptive gap in the respective legal bases will

Der Versorgungsanspruch des Patienten im Falle des Marktaustritts

▸ **Die Vorgaben des SGB V**

- Anspruch auf Einhaltung der gesetzlichen Vorgaben

„Anspruch auf eine verfassungsmäßige Ausgestaltung und auf eine grundrechtsorientierte Auslegung des Leistungsrechts der gesetzlichen Krankenversicherung zusteht (…). Gesetzlicher Ausgestaltung bedürfen insbesondere auch die grundsätzlich zulässigen (…) Verfahren zur Bewertung des diagnostischen und therapeutischen Nutzens sowie der medizinischen Notwendigkeit und Wirtschaftlichkeit neuer Untersuchungs- und Behandlungsmethoden. Würde eine zur Behandlung einer Krankheit benötigte Leistung in einem Entscheidungsprozess verweigert, der verfassungsrechtlichen Anforderungen nicht genügt, wären Versicherte in ihren Grundrechten verletzt."
(BVerfG v. 10.11.2015, 1 BvR 2056/12, Rn. 20)

Quelle: Prof. Dr. Stefan Huster

Das Bundesverfassungsgericht hat klargestellt, dass GKV-Versicherte Anspruch auf eine grundrechtsorientierte Auslegung des Leistungsrechts haben.

lead one to conclude that the legislature has delegated the task of ascertaining these „standards of evidence-based medicine" to the institutions performing the actual benefit assessment. Here, judicial control will not be able to provide anything other than plausibility tests. Correspondingly, the jurisprudence of the Federal Social Court of Germany also holds that the evaluations of the IQWiG are afforded a „legal presumption of the correctness of its assessments": „In light of the legal ascertainment of the neutrality and quality of the assessments ordered from IQWiG, the compliance with all statutory requirements establishes a legal presumption of accuracy of such an assessment, which, in cases such as this one, shall negate the necessity for further evidence gathering. This is inferred from the facilities, task and legal purpose of the IQWiG institution. With this in mind, assessments of the IQWiG conducted in compliance with the law are afforded a guarantee of correctness (BSG Ruling in 1/ 3. 2011 – B 1 KR 10/10 R, Rn. 74)

The SGB V will therefore hardly be suitable to determine that a benefit assessment was based on faulty methodical assumptions, and where price determination is concerned, Para. 130b Sec. 3 SGB V will at the very least provide a fixed upper price limit if such an assessment has concluded that no additional benefit has been proven. Simple law can therefore hardly offer legal remedy to those insured whose drugs have exited the market.

2. General constitutional regulations

The situation is similar for entitlements of the insured based in the fundamental rights of Germany – with the exception of the „Nikolaus cases", which we shall discuss shortly. As the German Federal Constitutional Court has reaffirmed in 2015, the freedom and service entitlements stipulate that „there is no constitutional right to specific services in the treatment of illnesses", so that the „proceedings for the assessment of the diagnostic and therapeutic benefit as well as the medical necessity and economic feasibility of new diagnostic and treatment methods" are „generally permissible" (BVerfG v. 11/10/2015, 1 BvR 2056/12, Rn. 20), this should easily be applicable to the early benefit assessment.

All that remains is an entitlement based on equality considerations on the legal basis of the equality clause of Art. 3 Sec. 1 of the basic law: According to it, the exclusion of a desired service must not be capricious compared to the services included in the service catalogue. Aside from the fact that this entitlement is not very assertive because it will frequently be possible to find reasons for a differentiating service exclusion, it also faces substantial hurdles in the drug assessment field. The reason is that the decision

Der Versorgungsanspruch des Patienten im Falle des Marktaustritts

- **Gleichheitsgrundrechtlicher Anspruch**
  - Ausschluss einer begehrten Maßnahme darf – im Vergleich zu den im Leistungskatalog enthaltenen Maßnahmen – nicht willkürlich sein
  - hier kaum operationabel, weil durch Entscheidung des PU gebrochen und Nutzenbewertungs- und Preisfindungsverfahren komplex und intransparent

Quelle: Prof. Dr. Stefan Huster

Die Maßgabe des Bundesverfassungsgerichts, dass der Ausschluss einer begehrten Maßnahme nicht willkürlich sein darf, wird in der Praxis nur schwer operabel sein.

of the pharmaceutical company to exit the market is the cause of the service exclusion; the institutions beholden to the basic law of Germany – IQWiG and GBA – are therefore only indirectly responsible. One would only be able to introduce equality considerations, insofar the benefit assessment or the offered price have individually deviated from the general principles, thereby „disadvantaging" one specific drug. However, this will be hard to prove, and requires at the least cross-indication clinical outcomes. In the practice of the law, such efforts will at best fail due to the complexity of the assessment processes combined with the lack of transparency of the price determination.

3. The special case of the „Nikolaus principles"

One judicial silver lining for the insured and patients whose drugs are no longer available might be provided by the „Nikolaus ruling" of the German Federal Constitutional Court on 12/6/2005 (BVerfGE 115, 25 et seq.). According to this – controversial – ruling, the insured can in individual emergency situations demand services from the SHI which would not be otherwise available pursuant to the general rules and regulations. The legislation has adopted this jurisprudence – in a slightly expanded form even – in Para. 2 Sec. 1a of the SGB V: „Policy holders with a life-threatening or frequently mortal illness or with an illness of at least comparable qualities for which no generally accepted treatment which complies with accepted medical standards is available, can demand services which deviate from Section 1 Sentence 3, if a not entirely unrealistic expectation of cure or a detectable positive effect on the course of the disease is present."

Does this affect the constellation of the market exit? One thing, however, cannot be the result, namely, that the benefit assessment is not performed or price negotiations will be forgone in order to pre-empt a market exit of treatments used for life-threatening diseases. It is only natural that the solidarity system has a vested and legitimate interest especially for highly priced „end of life" drugs to have their benefit assessed and their prices regulated. The rigorism of constitutional law cannot go so far that the SHI must rely solely on statements by the pharmaceutical company and accept their price expectations. This would be precluded by Para. 35a and 130b SGB V anyways. A conceivable way out is therefore a different one, namely, to import the drug no longer available in Germany after the market exit from abroad in individual cases and the assumption of the resulting costs by the insurance company when the „Nikolaus requirements" are met. Now a legal basis is established for the import in Para. 73 Sec. 3 of the German Medicinal Products Act, but how about the sick funds´ obligation to pay?

Here, one will first have to differentiate between the two aforementioned constellations. On one hand, it is possible and even common that the market exit is caused by the added benefit being considered not proven during the added benefit assessment, which will trigger the upper price

limits imposed by Para. 130b Sec. 3 SGB V. In these cases, one could take the position that an obligation of the sick funds to assume the costs would be „automatically" precluded in the event of later imports, because the benefit assessment has shown that there is no added benefit compared to the ACT, which would mean that the „Nikolaus requirements" were not met to begin with. However, such arguments may not meet the purpose of „Nikolaus".

First of all, one must not equate the ACT as defined by the assessment procedure to a „generally accepted treatment which complies with accepted medical standards" within the meaning of „Nikolaus". For example, when the IQWiG chooses „best supportive care" as ACT – which happens quite often – said ACT may have quite different therapy goals than the drug that has exited the market, which in itself would mean that they would be excluded under „Nikolaus" as „service compliant with medical standards". The benefit assessment furthermore leads to generalising statements on the added benefit, whereas the „Nikolaus principles" are based on the idea that in individual cases circumstances could be entirely different and must therefore be handled outside of the standard system of the SHI to regulate medical innovations.

Because – to state it again – the fact that the added benefit was not proven in a prescribed manner does not mean that there is no added benefit at all. It is particularly for that reason, that „Nikolaus" wants to lower the evidence requirements in emergency-like situations in such cases. Thus, one would have to say: Neither the negative results of the benefit assessment nor the fact that the market exit was ultimately the pharmaceutical company's decision negate the „Nikolaus claim".

On the other hand, it is also conceivable that an added benefit was proven in the benefit assessment procedure, but the pharmaceutical company does not agree with the offered or determined price and therefore exits the market. Here, the situation is somewhat easier, because it is already proven that there is an added benefit which supports the „Nikolaus claim". On the other hand, this legal consequence has very peculiar effects, because it would appear that it obligates the sick funds to pay a (high) price for the drug, which is explicitly not where the price negotiation proceedings have arrived.

However, this objection too is not sufficient to pre-empt the „Nikolaus claim". At its core, this is based in the fact that according to current jurisprudence and pursuant to Para. 2 Sec. 1a SGB V the claim is cost-indifferent. One may have good reasons to criticise this, however, in other „Nikolaus cases" beyond drug provision the courts – at least in their written reasons; one never really knows if the costs did not at least play a secondary role in the evaluation of the service requirements – have approved claims entirely without regard for the actual costs.

In 2013, for example, the Federal Constitutional Court deemed possible a „Nikolaus claim" for a non-approved „treatment with a combined immunotherapy (hyperthermia, oncolytic viruses and dendritic cells) by a general and naturopathy practitioner" with therapy costs of EUR 15,000 per month (!), without ever even considering the price a problem (BVerfG, NJW 2013, P. 1664 f.). To the cost assumption by sick funds for drugs which are no longer available in Germany this means that the sick funds indeed have to pay the price that has been accepted in the countries from which the preparation is being imported – even if the sick funds deem such pricing inappropriate. At best, the warranted economic feasibility results in an obligation of the pharmacy to choose the country with the lowest procurement price for the import.

Der Versorgungsanspruch des Patienten im Falle des Marktaustritts

- **Höhe der Kostentragungspflicht der GKV**
  - „Nikolaus-Anspruch" in Rspr. und § 2 Ia SGB V ist kostenunabhängig!
  - vgl. BVerfG 2013: nicht anerkannte „Behandlung mittels einer kombinierten Immuntherapie (Hyperthermie, onkolytisch Viren und dendritische Zellen) bei einem Arzt für Allgemeinmedizin und Naturheilverfahren" mit Therapiekosten von 15.000 Euro pro Monat(!)
  - daher auch hier Pflicht zur Übernahme der Kosten in erforderlicher Höhe
  - Grenze des Wirtschaftlichkeitsprinzips: günstigste Bezugsmöglichkeit

Quelle: Prof. Dr. Stefan Huster

Durch die Rechtsfolge des „Nikolaus-Beschlusses" ergibt sich, dass eine Krankenkasse einen hohen Preis für ein Arzneimittel zahlen muss, der dem Ergebnis des Preisfestungsfahrens gerade nicht entspricht.

IV. Possible solutions

1. Need for and levels of reforms

The critical discussion of market exits after drug benefit assessments as well as the „Nikolaus"-developments (in the drug area but also with respect to service types) demonstrate that a methodical EBM-rigorism will encounter political, ethical and also legal obstacles. Certainly of interest to those immediately affected (patients/insured, practitioners and payers), will be the practical consequence that a service is not available from the statutory health insurance. Whether this is justified in individual cases will, of course, always be disputed. The more fundamental problem though is the fact that the impression arose that normative political questions which would merit their own discussions are being „hidden" within relatively technical debates over the principles of method evaluations, thus evading the conversation. The provision of care in particularly urgent cases to which „Nikolaus" applies is a particularly obvious but not the only example of unclarified normative questions within the grey zone of not (yet) proven additional benefits.

It does seem clear though that the „Nikolaus import" is not very satisfactory in individual cases, and at best represents a safety valve rather than a general solution, even though that individual „tragic" cases and their respective need for a solution cannot be ruled out in any – however well regulated – healthcare system. The legislature has already responded to this situation outside of drug procurement with the „potential"-regulations set forth in Para. 137c Sec. 3 and 137e SGB V. If one were to consider such intermediary interim solutions for drug benefit assessments – which certainly cannot primarily be the task of the jurisprudence – they could be applied to the benefit assessment itself (2.) or to the price determination proceedings (3.).

2. Modifications to the benefit assessment

A corresponding „potential"-regulation applied to the assessment procedure for drugs would be a conceivable approach, however, it would be very difficult to implement this suggestion in a manner that would be satisfactory from a systemic perspective. One must furthermore consider that the various levels of the IQWiG assessments („proof", „note" or „indication" of an added benefit) already contain very similar differentiations. It must furthermore be considered if the inclusion of a clearing office which can arbitrate differences of opinion between the G-BA and the pharmaceutical company about assessment methodology would be a productive suggestion. The upper house of

parliament has already submitted this point in AMVSG negotiations, however, this measure would presumably only increase the number of actors and thereby reduce transparency. There is certainly a real need for regulation concerning the harmonisation of marketing authorisation and benefit assessment procedures. It cannot be that the marketing authorisation procedures are being accelerated while national assessment institutions respond with contempt in remarks – at that point in time – stating that high-quality studies are not yet available and that therefore the determination of an added benefit will be precluded to begin with. However, this harmonisation will not be easy unless one were willing to harmonise the entire HTA process across Europe.

From that perspective, it is quite odd just how small the role of the medical societies in these assessment procedures really is. On one hand, one would expect that their applied practical clinical expertise cannot be ignored. On the other hand, there may be various biases due to the proximity to the pharmaceutical companies.

3. Modifications to the price determination process

Yet other questions suggest approaches to the problem at the level of the price determination process instead of the assessment situation, addressing the payers and the pharmaceutical companies as negotiation partners along with the arbitration office. This is the level at which the AMVSG is now broaching the issue: Once it became clear that a confidentiality of reimbursement prices cannot be politically established, the strict linking of the price of drugs without proven added benefit to the cost of the appropriate comparative therapy were to be relaxed by converting Para. 130b Sec. 3 P. 2 SGB V into prescriptive ordinance. The flexibility afforded to the negotiating parties and the arbitration office in this manner is intended to also benefit already assessed drugs and drugs that have already exited the market. Pharmaceutical companies will have three months after the AMVSG goes into effect to submit corresponding applications (Para. 130b Abs. 7a SGB V).

Lösungsmöglichkeiten

- **Modifikationen der Nutzenbewertung**
  - „Potential"-Regelung?
  - Mediator (Bundesrat)?
  - Harmonisierung von Zulassungs- und Nutzenbewertungsverfahren?
    - Europäisierung der HTA?
  - Fachgesellschaften stärker einbinden?
- **Modifikationen der Preisfindung**
  - Vertraulichkeit der Preise (s.o.)?
  - Flexibilität der Preisfindung bei nicht belegtem Zusatznutzen (Soll-Regelung in § 130b III 1 SGB V idF des AMVSG-Entwurf)?

Quelle: Prof. Dr. Stefan Huster

Zwei grundsätzliche Reformebenen sind bei der Suche nach Lösungsmöglichkeiten zu unterscheiden: Änderungen bei der Nutzenbewertung und bei der Preisfindung.

4. Conclusion

This pricing-based solution implemented by the AMVSG may have preliminarily mitigated the problems surrounding drugs without proven added benefit, however, it remains to be seen how this will affect negotiations in practice. However, this constellation will remain work in progress, because at the time the early benefit assessment takes place there is often no sufficient information available to definitively confirm or deny an added benefit. Maybe over time models will have to be considered which initially accept lesser evidence levels, set temporary price levels, and then finalise the pricing once additional data is available.

Aspects of drug approval without sufficient evidence

Professor Dr. Karl Broich, Dr. Wiebke Löbker | Federal Institute for Drugs and Medical Devices

In the context of the drug approval process, randomised controlled trials (RCT) are the gold standard for the evaluation of the efficacy and safety of drugs. There are, however, certain scenarios in which methodical or ethical considerations make it impossible or inappropriate to conduct RCTs with a high degree of internal and external validity. At the same time though, it is desirable for innovative drugs for illnesses with currently insufficient treatment options to reach the patients as soon as possible. This article shall explore possible causes of the limited availability of efficacy and harm potential data, and also the challenges arising in the drug approval process due to the resulting uncertainties. It shall discuss the general regulatory options available when dealing with insufficient evidence.

Evidence in the drug approval process – the „gold standard" RCT

The evaluation of the risk-benefit ratio is the core element of the drug approval process for drugs. A positive approval decision can only be arrived at when clinical trials have shown that a determined medical benefit – meaning therapeutic efficacy – outweighs known and/or potential risks, namely, adverse effects.

In the evaluation of the efficacy and safety of a drug, randomised and controlled clinical trials – meaning Phase III confirmation trials – are, due to their methodical design, an ideal instrument to answer the question of a causal link between the therapy option on trial and its efficacy. Based on preclinical data and clinical data obtained in Phase I and II, pivotal studies undertake a comparison to current standard therapies. If no suitable measures are available, a comparison to placebo is acceptable [1].

For certain indications it is necessary to prove an advantage over placebo when a high and variable placebo-response-rate can be expected (e.g. indication pain). In this scenario, a confirmation study should prove the superiority over placebo as well as provide an active comparison to a therapy standard of known efficacy, in order to provide a context to the measured difference to placebo and to facilitate an evaluation of the clinical relevance of these identified differences [2].

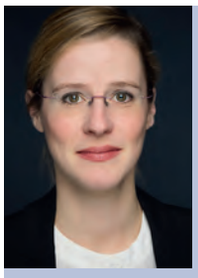
As the study cohort substantially affects the indication, prespecified inclusion and exclusion criteria should define a potential patient population which is representative of the actual target population.

The randomised assignment of patients to therapy groups ensures structural uniformity and thereby – aside from assisting in the blinding of the study – helps to prevent systemic errors.

The determination and weighting of suitable clinically relevant endpoints for efficacy evaluation are particularly important in the planning phase of a clinical trial. The primary endpoint determines the statistical evaluations, the required number of cases for sufficient reliability and the criteria which would trigger a premature study abortion. Endpoints are often coordinated with the respective authorising authorities in the early planning stages of clinical trials. Depending on indication, clinical parameters (such as survival rate, pain reduction) immediately relevant to the patient or surrogate parameters (e.g. lab parameters such as HbA1c, blood pressure) are acceptable as predictors of other more conclusive parameters, as long as there is a causal link between the surrogate and the actual outcome.

In the evaluation of benefit-risk-ratios, the methodical advantages and resulting reliability of the results of randomised controlled clinical trials with clinical endpoints are, however, not without certain disadvantages. Accordingly, they can be meaningfully augmented with additional data (e.g. from comparative non-randomised studies, non-comparative one-armed studies or from registries), or, in particular therapy situations with an extensive medical demand and a lack of alternative therapies, even replaced.

There can be, for example, limitations to the applicability of study results to the actual „real world" clinical application. RCTs are conducted in select study centres which may only consider the therapy standard (under ideal conditions) common in a given locality. The patient population included in a clinical trial is usually kept relatively homogenous by determining inclusion and exclusion criteria with regard to diagnostic criteria and disease progression. This is done because it is quite difficult to document statistical group differences in very heterogenous patient populations. However, this selected study population only reflects a limited section of the actual patient population requiring treatment (high internal validity, low external validity). For



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example, patient populations are limited based on the severity of the disease, potential prior treatments and concomitant medications or even based on patient age. The approved indication is usually based on the conditions examined in the trial, an extrapolation for the (entirety) actual target population or other concomitant drugs requires an explicit justification.

On the other hand, the framework of an RCT provides a much tighter monitoring and control of the patient, and prior treatments and concomitant medications are identified much more thoroughly and comprehensively than is common in daily clinical practice. As a result, the spectrum and scope of proven adverse events and drug interactions is limited. The proof of a statistically significant difference in favour of the tested therapy obtained in the course of a randomised and controlled study requires large case numbers. However, such large numbers are not always available in all therapy situations.

Various clinically relevant endpoints are only revealed in the later course of a study and require long study durations. In the event of illnesses with a high unmet medical need for which no sufficient therapy options are available, this is, however, juxtaposed to the efforts [3; 4] to improve the development of innovative drugs and to accelerate the availability of such drugs to patients once a positive benefit-risk-ratio has been established. This applies, for example, to many oncological indications and to rare orphan diseases. For example, by providing early scientific consultation and support the PRIME-initiative of the EMA [5] aims to optimise development programmes, prevent bad regulatory decisions, and to more efficiently apply existing regulatory measures such as the options of accelerated assessment and conditional approvals, in order to keep meeting the requirements of approving authorities while also meeting the needs of the affected patients.

Causes of unreliable evidence

Although randomised controlled clinical trials provide the standardised required evidence for approvals, there are still scenarios in which generating meaningful statistically significant results is impossible or only possible to some limited extent. Particularly for rare diseases or in vulnerable patient populations (i.a. children/youth, late stage diseases) the patient pools are often very small. In this scenario, the number of cases required for a randomised controlled clinical trial which can prove a significant advantage of the tested preparation with respect to clinically relevant endpoints (e.g. mortality) cannot be provided. Here, it is at best possible to demonstrate a numerical advantage („trend"), or alternatively, surrogate parameters are utilised.

The use of surrogate parameters has certain practical advantages over the determination of the actual clinically relevant outcome, such as reduced trial durations, when the surrogate parameter can be directly measured as a risk factor in place of an event which would require longer progress monitoring and a corresponding reduction of case counts. A prerequisite, however, is the valid and proven establishment of the causal link between the surrogate and the actual endpoint.

However, the example of the antiarrhythmic drug Flecainid used to treat ventricular extrasystoles clearly shows that surrogate parameters are not always sufficient to come to sufficiently valid conclusions about clinically relevant endpoints: The marketing authorisation granted by the US FDA was based on results obtained from the parameters arrhythmia/extrasystoles, because a strong correlation between the surrogate and cardiac mortality has been postulated. Furthermore, conducting a clinical mortality study was deemed to be unnecessary and unethical. After the marketing authorisation was granted, the results of the Cardiac Arrhythmia Suppression Trial (CAST) then showed

that Flecainid did, despite a pronounced reduction of extrasystoles, actually cause higher mortality [6]. Thus, the hypothesis that a normalisation of pathophysiological (lab-)parameters can prevent or reduce the long-term effects of an illness cannot always be confirmed. The use of surrogate parameters is therefore always subject to certain uncertainties, especially in the absence of comprehensive validity data.

The advantages of an accelerated availability of needed therapy forms afforded by the options of shorter trial durations and/or reduced case numbers must be weighed against the risk of initially neglecting long-term effects and to approve an ineffective medicinal product with respect to the clinically relevant endpoint.

In therapy situations characterised by a substantial unmet medical need, e.g. in oncological indications, the applications for marketing authorisation are at times initially based on phase-II-trials which have demonstrated a positive benefit-risk-ratio based on the collected surrogate data points such as the response rate. However, the correlation with the mortality endpoint cannot always be confirmed.

For the active ingredient Vintafolid (Vynfinit), for example, which is used to treat patients suffering from platinum-resistant ovary carcinomas, a randomised and controlled phase-II-trial showed a high response rate. An interim analysis of the randomised double-blind phase-III-trial which was underway at the time, however, was not able to find an advantage of Vintafolid. At the time, the application for marketing authorisation was withdrawn before the decision.

In the case of the active ingredient Crizotinib (Xalkori), a conditional approval was granted for the treatment of previously treated anaplastic-lymphoma-kinase (ALK)-positive advanced non-small cell lung carcinoma based on the data of the uncontrolled phase-I/II-trials. Here too, the crucial factor were the high response rates (53 to 60 percent) and the positive results regarding progression-free survival rates (8.5 to 9.2 months median).

Unlike with Vintafolid, these preliminary efficacy results could consistently be confirmed across two uncontrolled studies and also in a direct comparison with Pemetrexed in the course of a randomised and controlled phase-III-study which was underway at the time of the approval, and furthermore in additional studies conducted with additional patient cohorts (patients without prior treatment and patients with ROS1-positive non-small cell lung carcinoma). Thus, the initially conditional approval of Crizotinib did not only lead to a regular marketing authorisation but actually to an expanded approval.

Due to the absence of causality evidence, additional uncertainties arise when results are presented which were generated by non-randomised studies and non-comparative (single-armed) studies. Here, the observed effect cannot be immediately linked to the tested substance due to the absence of a comparison or a lack of comparability of the therapy groups.

Prior experiences have shown that development programmes targeting large populations can fail if the cohort selection was faulty. On one hand, this may be due to different patient characteristics, on the other, some diseases which appear to be phenotypically identical can have different sources and progressions. Since no statistically significant difference favouring the tested treatment can be found, the decision is made to abandon the development of such a medicinal product. It is possible, however, that such active substances can be effective and safe in subpopulations which have been identified with prespecified markers (e.g. companion diagnostics), even though they may not be suitable for general broad application.

General options with insufficient evidence

If the data submitted with the marketing authorisation application does not warrant the assumption of a positive benefit-risk-ratio, approval must be denied.

There are, however, various options and methods available to handle the evaluation of efficacy and safety in uncertain or incomplete data situations when a positive benefit-risk-ratio is assumed, which do not require that needed therapy options are being withheld from patients.

For example, a conditional approval or respectively an approval with attached conditions can be granted when such an approval can close a supply gap, even before comprehensive clinical data regarding the safety and efficacy have been submitted. In the case of a conditional approval granted on the basis of early data from (ongoing) clinical trials with surrogate parameters as predictors of the clinically relevant outcomes, additional comprehensive clinical analyses of the safety and efficacy must be submitted in order to confirm a well-balanced benefit-risk-ratio. Ideally, this will be data obtained from randomised controlled studies. However, additional randomised controlled clinical trials are often difficult to realise due to the marketing authorisation with general availability. Thus, it is possible that non-randomised or non-comparative trial data or respectively „real-world-data“ can augment the results of the clinical trial.

US FDA Sentinel programme [7] data suggests that „real world data“ cannot only be very helpful in adverse effect and risk signal detection, but much rather that when a certain amount of data is available, indications of the efficacy of a drug can also be derived. This, in turn, means that limited pivotal trial data can be augmented with such data. There is furthermore an opportunity to include additional data into the risk-to-benefit evaluation by running complex statistical models.

When non-controlled studies are submitted, it is possible to review to what extent historical controls can be integrated in the efficacy and safety evaluation, as these at least allow statements regarding the progression of the disease without treatment or when alternative therapy options are used. This data, however, is in itself burdened by limitations, as the respective patient cohorts and study protocols can be very heterogenous. Furthermore, there is a tendency to prefer positive results for publication, which makes it impossible to rule out a selective distortion of the data („publication bias“).

Another factor is that the results can be used to extrapolate expanded patient cohorts. This can, for example, include the application of evidence to different age groups, provided it can be proven that the source- and target population are sufficiently comparable with respect to the disease to be treated (pathophysiology, clinical manifestation, disease progression), mode of action, clinical response and the suitability of efficacy- and safety endpoints.

Conclusion

In the assessment of the efficacy and safety of a medicinal product, conclusive evidence from high-quality randomised controlled clinical trials concerning the immediate clinically relevant endpoints compared to established reference substances is not always available. There are many sources of insufficient evidence. In order to not withhold new treatment options from patients in therapy situations with a great unmet medical need or respectively to not unnecessarily delay access to innovative treatments, it is necessary to thoroughly evaluate the existing uncertainty and the risk of a false positive decision vis-a-vis the need to accelerate the availability of a new drug. Various options are available, e.g. a conditional approval in which the marketing authorisation granted to close a supply gap is initi-

ally based on preliminary data, which must then be augmented with additional data on the safety and efficacy of the drug to be submitted at a later time after the initial approval. Furthermore, there are programmes such as the EMA's PRIME-initiative, which aims to improve the development of drugs for severe diseases i.e. by providing early consultation and support. The initiative can furthermore contribute to an improvement of the evidence by optimising development protocols.

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Benefit assessment of orphan drugs despite insufficient evidence and absence of RCT

PL Dr. Michael Kulig | Federal Joint Committee (G-BA)

In early benefit assessments, the potential „incentive" created by special orphan drug regulations to obtain approval based on studies with limited evidence, resulted in the identification of a non-quantifiable additional benefit in more than half of the 49 prior proceedings. Compared to non-orphan drugs, it is more common to see insufficient evidence due to surrogate endpoints and non-comparative trials. It is in the nature of non-controlled studies to have a higher bias potential. Methodical proceedings such as statistical adjustment cannot compensate for limiting factors such as structural incompatibility or bias due to different data collection timing when historical controls are applied. This applies regardless of the type of the data source used as substitute for the generation of non-randomised controls. Even when data from such sources is similarly prospective, of high quality and possibly obtained by a procedure comparable to a trial protocol, one must still assume a low reliability when such data is used for early assessments.

Special European Union directives afford drugs for rare diseases (orphan drugs) certain advantages in the marketing authorisation process and market access in general [1]. The early benefit assessment at the Federal Joint Committee (G-BA) also has relaxed requirements on the process of determining added benefits compared to drugs without orphan drug status (non-orphan drugs).

One might consider these special regulations to be helpful and an incentive to develop drugs for rare diseases for which there are no or not yet sufficient therapy options available. However, the resulting potential „incentive" to apply for and obtain marketing authorisation based on trials with limited evidence should be considered problematic.

According to the Regulation on Medicinal Products for Rare Diseases of the European Parliament, „patients with rare diseases have the same right to good treatment" and „the same entitlement to the safety and efficacy of medicinal products as other patients" (excerpt from the second and seventh recitals of European Directive [EC] 141/2000).

The criticism of studies with limited evidence refers to the evidence gaps and/or low quality of the evidence of these trials submitted to the approving authorities or respectively for the assessment of added benefits by the G-BA. These limitations do not apply to all orphan drugs equally.

Compared to marketing authorisation trials of non-orphan drugs, the pivotal trials for orphan drugs are disproportionately non-comparative trials or non-randomised trials respectively [1, 2, 3]. Even though evidence-based medicine and the approving authorities consider randomised controlled trials (RCT) to be the methodical „gold standard" providing the highest evidence quality and result reliability [5]. This imbalance is also seen in the use of surro-

Nicht validierte Surrogate als primäre Endpunkte in Zulassungsstudien zu seltenen Stoffwechselerkrankungen. Konsequenz bei früher Nutzenbewertung im G-BA: Endpunkte nicht bewertungsrelevant für Zusatznutzen (Ausnahme: Cortisol bei Pasireotid, Beschluss im Jahr 2012)

Wirkstoff	Erkrankung	Surrogat als primärer Endpunkt
Alipogentiparvovec	Lipoproteinlipase-Defizienz	*Triglyceride*
Asfotase	Hypophophatasie	*Knochenmineralisierung*
Migalastat	lysosomale Speicherkrankheit (Morbus Fabry)	*Glomeruläre Filtrationsrate*
Nintedanib	idiopathische pulmonale Fibrose (IPF)	*Vitalkapazität der Lunge*
Pasireotid	Hypophysendysfunktion (M. Cushing)	*Cortisol*
Sebelipase alpha	Mangel an lysosomaler saurer Lipase	*Alanin-Aminotransferase*

Quelle: https://www.g-ba.de/informationen/nutzenbewertung/

Tabelle 1: Bei der Nutzenbewertung im G-BA wurden die Endpunkte als nicht bewertungsrelevant angesehen. Ausnahme ist der Beschluss im Jahr 2012 zu Cortisol bei Pasiretoid.

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gate endpoints of questionable patient relevance [2, 3, 4]. Just how these two aspects of insufficient evidence are being handled in early benefit assessments and what implications result from them shall be demonstrated by example in this article [6]. Up until 1 March 2017, 49 orphan drugs have been assessed with the G-BA proceedings having concluded with a determination of an added benefit. Aside from the most common primary surrogate endpoint progression-free survival, surrogates have mainly been used as primary endpoints in trials for rare metabolic disorders. In the vast majority of cases, these surrogate endpoints have not been validated as „replacement endpoints“ for a patient-relevant endpoint. Examples are listed in Table 1.

Unlike the approval authorities, which base their efficacy decisions in such cases on the primary approval trials mainly on the assessment of the primary (surrogate-)end-

point, the G-BA considers these endpoints as not relevant to the assessment if the surrogate as not sufficiently validated. In this scenario, the benefit assessment does indeed reflect the endpoint for the purpose of making informed statements and to be able to make an informed decision regarding the added benefit. However, the endpoint is not used in the general assessment of the scope of the added benefit.

In light of the intended relaxed authorisation requirements (think „Adaptive Pathways" in Europe and „21st Century Cure Act" in the US), critical voices from within the scientific community which question the use of surrogate endpoints are on the rise [7]. A commentary recently published in a prestigious medical journal regarding an unusual and extremely rare approach conducted by the US Food and Drug Administration (FDA) clearly illustrates that surrogate endpoints are controversial and critically discussed at approval authorities too [8]. The article was prompted by an assessment of the primary endpoint of the approval study for a new active substance for the treatment of the rare Duchenne muscle atrophy.

The validity of the primary surrogate endpoint, a protein found in muscle biopsy samples, with respect to the clinical benefit was evaluated critically by all involved scientific investigators of the FDA. In the final approval decision, they were overruled by the director in charge. This prompted the investigators to lodge a complaint with the superordinate arbitration body, however, the marketing authorisation was upheld. In other trials conducted by the G-BA for the early benefit assessment of another substance intended for the treatment of Duchenne muscle atrophy, on the other hand, the primary collected endpoint was the ability to walk – and endpoint the G-BA considers patient-relevant.

When considering that publications note an observed aspect of a low proportion or even complete absence of RCT evidence in orphan drug proceedings, it becomes apparent that in the 49 early benefit assessments conducted since 2011 the pivotal studies, which are the basis of the benefit assessment, are non-comparative studies (see Table 2). Such non-controlled trials have an inherent distortion potential and therefore a lower result reliability than RCTs, thus complicating valid conclusions about the scope of the added benefit. With the exception of one case (Pasireotide [M Cushing]), this low result reliability of non-controlled studies always results in a non-quantifiable added benefit. This exception, however, did also concern one of the first orphan drug proceedings in 2012.

In the debate about the lack of RCT evidence in orphan drugs, one often hears the argument that the rarity of the disease makes RCTs and respective comparable studies impossible. Notwithstanding the fact that a European Directive enshrines the entitlement of patients with rare diseases

Studiendesign der bisherigen 49 Orphan Drug-Verfahren

Studiendesign	Anteil
Vergleichend (parallel-prospektiv)	76 %
Randomisierte Zuteilung	*74 % (davon 10 % Nicht-unterlegenheitsstudien)*
Unkontrolliert/einarmig	22 %
Literatur-Review	2 %

Quelle: https://www.g-ba.de/informationen/nutzenbewertung/

Tabelle 2: Bei jedem vierten Orphan Drug sind die pivotalen Studien, die die Basis der Nutzenbewertung bilden, nicht-vergleichend.

Fragliche Argumente gegen die Durchführbarkeit von RCTs bei seltenen Erkrankungen anhand von Beispielen der Orphan Drug-Nutzenbewertungsverfahren beim G-BA (Stand 1. März 2017)

Fragliche Argumente	Beispiele aus G-BA Verfahren
Geringe Anzahl von Patienten bei seltenen Erkrankungen	
Große Spannweite der in Zulassungsstudien eingeschlossenen Patientenzahlen (N=17 bis N=929)	N<50 Studienpatienten: 3 Verfahren • N=17 (unCT): Lipoproteinlipase-Defizienz [Alipogentiparvovec] • N=49 (Fallserie): Angeborene Störungen der primären Gallensäure-synthese [Cholsäure] • N=42 (CT): Kurzdarm-Malabsorptionssyndrom [Teduglutid] N=929 (RCT): Multiples Myelom [Carfilzomib]
Anzahl der für die Behandlung infrage kommenden Patienten allein in Deutschland (N_{GKV})*	N_{GKV} = 7–35 [Lipoproteinlipase-Defizienz] N_{GKV} = ca. 600 [Hämophilie B**] → trotzdem kein RCT! N_{GKV} = ca. 2300 [Multiples Myelom***] → trotzdem kein RCT! N_{GKV} = 4700-7000 [Multiples Myelom****]
Rasch-progredienter, schwerer Verlauf	invasive Aspergillose (RCT mit aktiver Kontrolle!)
Trotz alternativer Therapien: unkontrollierte nicht-vergleichende Studien oder nur Vergleich gegen Placebo	z.B. Hämophilie, pulmonal arterielle Hypertonie, M.Cushing, Multiples Myelom und weitere Krebserkrankungen

* N_{GKV}: Anzahl der Patienten der für die Behandlung infrage kommenden Patientengruppen für Zielpopulation in der gesetzlichen Krankenversicherung (GKV) lt. Beschusstext bzw. Tragenden Gründen des G-BA (s. Website https://www.g-ba.de/informationen/nutzenbewertung/)
** Albutrepenonacog alpha, Beschluss 1.12.2016 und Eftrenonacog alfa, Beschluss 15.12.2016
*** Daratumumab, Beschluss 1.12.2016
**** Carfilzomib, Beschluss 19.1.2017
Abkürzungen: unCT: unkontrollierte Studie; CT: kontrollierte Studie (keine randomisierte Gruppenzuteilung); RCT: randomisierte kontrollierte Studie;

Quelle: https://www.g-ba.de/informationen/nutzenbewertung/ (Stand 1. März 2017)

Tabelle 3: Das Argument, aufgrund der Seltenheit sei keine vergleichende Studie möglich, ist wenig nachvollziehbar.

to safe and efficient medicinal products, a review of prior orphan drug proceedings at the G-BA makes this type of argument hardly compelling at all (see Table 3).

The following shall discuss two examples of lacking RCT evidence. These two non-controlled single-arm studies shall, as an example, illustrate the associated methodical

problems and how the G-BA handles them.

In the first example, the pharmaceutical company has only conducted a single-arm study with N=106 patients, despite the fact that a large number of potential patients (previously treated myeloma patients) was available in the target population. Due to the non-existence of controls, the pharmaceutical company submitted an indirect comparison by using control patients from other clinical trials (see Figure 1). However, such adjustments cannot replace an actual randomisation. Furthermore, even after adjustment the difference of therapy effects between the new drug and the historical controls did not reach a magnitude that would allow to rule out that the observed effects were solely caused by systemic distortion or coincidental diagnoses. The G-BA therefore does not consider the submitted indirect comparison to be suitable evidence of an added benefit. Due to the inherently low result reliability of non-controlled trials and the insufficient scientific data situation, the G-BA – simply from a legal perspective alone – classified the scope as non-quantifiable, even under consideration of the severity of the disease and the therapeutic objective of the treatment of the disease [9].

The second example is based on a metabolic disorder (lysosomal acid lipase deficiency [LAL]). A mildly progressing form of the disease affects older children and adults. The pharmaceutical company conducted a placebo-controlled RCT. The other substantially more severe form called Wolman-Disease affects infants and toddlers. Here, the pharmaceutical company conducted a single-arm clinical trial with toddlers. The feasibility of an RCT is debatable

1. Beispiel: Unkontrollierte Studie

Daratumumab (Multiples Myelom, $N_{GKV} \approx 1.900$)

Einarmige Studie (N = 106 mit mind. 3 Vortherapien), Monotherapie

Kein RCT

- **Hersteller: Matching-adjustierter indirekter Vergleich (MAIC)**
  - kein Register vorhanden → Daten für Kontrollen aus anderen klinischen Studien
  - Daratumumab-Patientencharakteristika werden durch Gewichtung denen der Kontrollen angepasst (vergleichbar wie beim „Propensity Score“ Verfahren)
- **G-BA identifiziert Limitationen:**
  - MAIC: kein adjustierter indirekter Vergleich im Sinne von indirekten RCT-Vergleichen
  - Relevante Unterschiede der Studien- und Patientencharakteristika, die auch durch Adjustierung nicht behoben werden können (z.B. Vortherapien, Erhebungszeitpunkte)
  - erhöhte Ergebnisunsicherheit → Effekte nicht in einer Größenordnung, bei der ausgeschlossen werden kann, dass diese allein auf systematischer Verzerrung beruhen

Quelle: Gemeinsamer Bundesauschuss
1. Tragende Gründe Daratumumab, 1.12.2016: https://www.g-ba.de/informationen/nutzenbewertung/234/#tab/beschlüsse

Abbildung 1: Adjustierte indirekte Vergleiche können nicht tatsächliche Randomisierung ersetzen.

due to the severity of the disease's progression and its rarity. However, this example too illustrates just how unreliable the results of non-controlled comparisons are (see Figure 2).

Uncertainties arose in the specification of the patient population included in a trial of the new active substance Sebelipase alpha, since the inclusion criteria for Wolman-disease were not defined with sufficient specificity (e.g. despite the fact that LAL-deficiency of the Wolman phenotype is characterised by a total or almost total absence of LAL-activity, only a nonspecific LAL-deficiency was required; also, the facultative inclusion criterion of gene mutations which were not comprehensively specified did not allow a differentiation between the two forms of LAL-deficiency). As no additional data from other clinical trials or a registry was available, the pharmaceutical company conducted an indirect comparison based on historical case series which the company collected retroactively. The comparability of the trial patients to historical controls was therefore questionable, with the result that the effect was potentially distorted in favour of the substance due the patients included in the clinical trial.

This was illustrated by the differences in age and mortality: at the time of the first administration of Sebelipase, all toddlers in the study were, naturally, still alive, whereby in the historical control groups half of the patients had already deceased at a comparable point in time (median age at first administration of the new substance: 2.99 months vs. median age at death of the controls: 3.0 months). Due to the low result reliability caused by insufficient evidence,

2. Beispiel: Unkontrollierte Studie

Sebelipase alpha (Mangel an Enzym Saure Lipase, $N_{GKV} \approx 5$)

Einarmige Studie (N = 9 mit Wolman-Krankheit, schwerer rasch-progredienter Verlauf)

Kein RCT

- **Hersteller: Nicht-adjustierter indirekter Vergleich anhand historischer Kontrollen**
  - kein Register vorhanden → retrospektive Fallserie (N=25) aus medizinischen Unterlagen von 18 Zentren in sechs Ländern
- **G-BA identifiziert Limitationen:**
  - Einschlusskriterien in Sebelipase-Studie nicht eindeutig für Wolman-Krankheit
  - Patienten mit besserer Prognose in Sebelipase-Studie eingeschlossen

	Sebelipase	Historische Kontrollen
bei erster Gabe von Sebelipase	N=9	N=25
Alter (Median)	2,9 Monate	3,0 Monate (Sterbealter!)
Mortalitätsrate	0 %	50 %

Quelle: Gemeinsamer Bundesauschuss
1. Nutzenbewertung Sebelipase-Studie, 4.1.2016: https://www.g-ba.de/informationen/nutzenbewertung/196/#tab/nutzenbewertung

the G-BA classified the magnitude of the added benefit as non-quantifiable [10].

Based on the aforementioned questionable arguments against the feasibility of RCTs as well as on the high proportion of RCTs (74 percent) in prior proceedings, one may assume that a lack of RCT-evidence can, in many cases, not be caused by the rarity and severity of the disease. Much rather, it might be based on a pragmatic and strategic decision of the pharmaceutical company, which is favoured by the approval authorities which grant approval based on indirect parallel comparative trial data.

Under circumstances such as severe, rapidly progressing and quasi-deterministic progressions, which may speak for difficulties in the feasibility of (R)CTs, individual cases can warrant that non-controlled or indirect comparative studies can be included in the considerations. The illustrated examples do, however, demonstrate that effects regarding the safety and efficacy identified with such trial designs produce a low result reliability. Methodical proceedings such as statistical adjustment cannot compensate for limiting factors such as structural incompatibility due to a lack of randomisation or bias due to different data collection timing when historical controls are applied. This applies regardless of the type of the data source used as substitute for the generation of non-randomised controls.

Even comprehensive data obtained in day-to-day healthcare practice, such as the British Clinical Practice Research Datalink (CPRD) or from disease registries, which are named as suitable data sources, are subject to the same potential bias mechanisms demonstrated in the presented examples. The primary objectives of such external data sources are, naturally, not the same as those of trials conducted during early benefit assessment, in which conclusions about the therapy effects of the tested drug must have a highest-possible degree of validity. Registries can provide long-term data gathered after marketing authorisation, especially safety-related data such as rare adverse events. Even when data from such sources is similarly prospective, of high quality and possibly obtained by a (registry-)protocol comparable to a trial protocol, one must still assume a low reliability when such data is used for early assessments. Consequently, the G-BA cannot quantify the added benefit.

Overall, however, the G-BA has in previous proceedings determined a non-quantifiable added benefit due to scientifically insufficient data not only in cases of non-controlled trials, but rather in over half of all cases (34 of 57 therapeutic indications) (see Figure 3). Reasons for evidence not

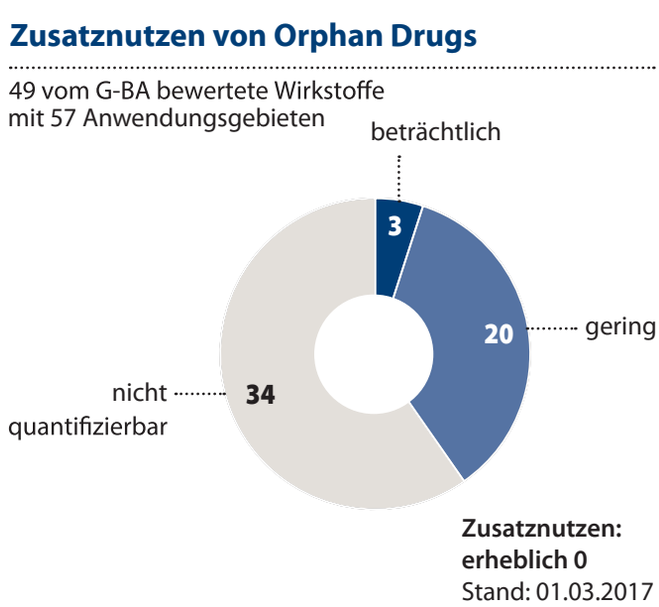

Abbildung 3: Da einige Verfahren mehr als eine Indikation bzw. Anwendungsgebiete beinhalteten, resultierten daraus 57 Einstufungen zum Zusatznutzen.

being sufficient for a quantification can, on one hand, be deficiencies in the trial design and/or the trial data, which are not solely based on the rarity of the disease but can also occur in trials of non-orphan drugs [11, 12].

On the other hand, the assessment of the added benefit can be impeded when RCTs – despite therapy alternatives – used placebo for comparison [Migalastat, Macitentan, Eliglustat]. The assessment is equally limited when superiority studies [Migalastat, Pitolisant, Eliglustat, Isacovunazol] were conducted that failed to establish a superiority over the comparator. These limitations complicate a valid and durable determination of the added benefit, thereby preventing – due to limited evidence – the G-BA from quantifying the added benefit. This furthermore leads to decisions often being made with a limited term with the condition that additional data will be submitted (12 restricted approvals out of 49 proceedings).

Conclusion

• The G-BA has determined a non-quantifiable added benefit in almost 60 percent of the orphan-indications assessed so far.

• Reasons for scientific data not being sufficient for a quantification include among general trial limitations the use of surrogate endpoints and the use of single-arm non-controlled studies.

• Low result reliability of non-controlled trials despite the use of external (historical) controls and registries, observational studies or other sources despite adjustment procedures.

• Handling by the G-BA when reliability is low

– with the exception of one case all „non-quantifiable“ added benefit

– Restrictions and lower classification of the magnitude of the added benefit

– Conditions when evidence is insufficient: Positive effect is to be confirmed.

• Randomised controlled trials are

– feasible even for orphan drugs and to be specified as gold standard

– In almost three quarters of the assessments RCTs were available.

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RABBIT RA-Register results – relevance for patient care

Prof. Dr. Angela Zink | Deutsches Rheuma-Forschungszentrum Berlin and Clinic for Rheumatology and Clinical Immunology, Charité

The RABBIT-registry (Rheumatoid Arthritis – Monitoring Biologics Therapy) monitors since 2001 approx. 16,000 patients with rheumatoid arthritis entering a biologic/biosimilar or conventional synthetic therapy for five to ten years each. RABBIT complements the evidence obtained from clinical trials with data regarding the safety and efficacy under real-life conditions. The initially feared increased cancer risk can now mostly be ruled out. RABBIT has firmly established the substantial impact of high disease activity on the incidence of secondary complications such as myocardial infarction, stroke, heart failure and premature mortality. With the RABBIT risk score for severe infections the risks associated with specific therapies can be weighed against the risks inherent to the disease. This serves as support to informed clinical decision-making.

Background of RABBIT

1. When the first two biologics – the TNF-inhibitors Etanercept and Infliximab – were approved for the treatment of rheumatoid arthritis (RA) in 2001, convincing data regarding the efficacy and short-term safety of these new substances was obtained in clinical trials, however, there was no experience whatsoever regarding the long-term application. Particularly the risks of severe infection, malignoma, new autoimmune diseases or the effect on the cardiovascular risk and mortality could not be properly foreseen. Conversely, the question of whether to date unknown and rare risks caused by the intense immunosuppression would be increased could not be answered. Thus, the rheumatological medical societies in several European countries pushed for the establishment of epidemiological long-term observational studies – the so-called biologics registries.

The largest registries, which closely cooperate since 2003, are located in the United Kingdom, Sweden and Germany. They meet annually to biannually and hold an additional biannual Register Congress under the auspices of the European Association of Rheumatologists. The German biologics registry RABBIT (Rheumatoid Arthritis – Monitoring Biologics Therapy) is located in the German Rheumatism Research Centre Berlin (DRFZ). Additional registries maintained at the DRFZ in the epidemiology department are JuMBO (young adults with juvenile idiopathic arthritis), the pregnancy registry Rhekiss (pregnant women with any of the inflammatory-rheumatoid diseases and their kids) and the RABBIT-SpA registry established in 2017, which includes patients with inflammatory spinal diseases and psoriatic arthritis. All these registries share the common task of investigating the long-term safety and efficacy of drug therapies in the context of the risks associated with the respective clinical picture.

1.1 Structure and objectives of RABBIT

RABBIT can include RA patients commencing therapy with approved biologics, biosimilars or JAK inhibitors, or as control group with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) when at least one prior csDMARD has failed. For each patient, physicians document the clinical status, therapy details and undesired effects in predetermined intervals (at therapy commencement, after three and six months and then semi-annually) for a period of at least five and if possible up to ten years. The patients report their subjective disease burden, ability to work and utilisation of the healthcare system. By now, more than 15,600 patients have been included which have in turn generated more than 60,000 patient-years of data (see Figure 3). Approximately 300 rheumatologists from all across Germany contribute to the registry.

The objective of RABBIT is to document clinical decision-making situations and to provide practitioners with information about the comparative safety and efficacy of therapy alternatives. Within this objective, one of the most demanding methodological tasks is to properly deal with the inevitable indication bias, meaning the reality of different risk structures within the therapy arms. To this effect, comprehensive work has been conducted in RABBIT which is considered exemplary for other registries. RABBIT works with methodological standards for the completeness and correctness of the data which approximate the standards of clinical trials.

One important quality criterion is the low rate of patients for which no information is gathered in the course of the observation. The rate is currently less than three percent. The completeness of the statements gathered on clinical questionnaires is also high due to intensive demands. Conducting such a study is cost- and staff-intensive. The team at the DRZF is comprised of multiple practitioners, statisticians and medical documentation officers.

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1.2 What is a registry?

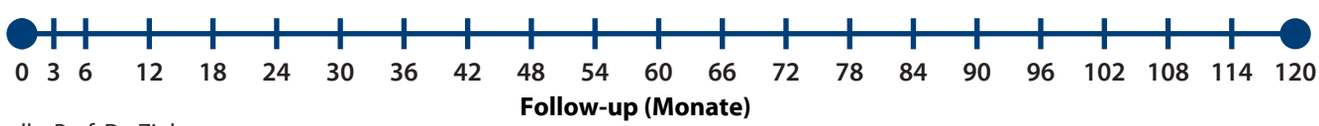
The term „registry" can conjure up misunderstandings regarding the type of the study. In 2001, we have chosen this term in coordination with other European countries, in order to clarify that we (unlike clinical trials) investigate the safety and efficacy of substances after marketing authorisation in non-selective patient populations. The current use of the registry term regardless of therapy is more in line with cancer registries, which aim for a wide but relatively superficial coverage of patients with the objective of being able to also identify regional differences regarding access or outcome; or, in line with those registries that are required in the course of the accelerated approval process for orphan diseases.

In contrast, RABBIT is a clinical cohort study for a wide

RABBIT – Langzeit-Kohortenstudie: Patienten mit rheumatoider Arthritis und Therapiestart nach Therapieversagen

2001	2003	2007	2009	2015	2016	2017
Enbrel Remicade	Humira (Kineret)	MabThera Orencia	RoActemra Remicade	Inflectra Remsima	Benepali	Flixabi Olumiant Xeljanz

Kontrollgruppe:
Synthetische DMARDs nach Therapieversagen



Quelle: Prof. Dr. Zink

Abbildung 1: Einschluss aller neuen Therapien ab Zulassung, Erhebungsdimensionen und Messzeitpunkte.

Individuelle Verlaufsdokumentation 5 – 10 Jahre

▸ **Arzt u.a.:**
- Krankheitsaktivität, Schweregrad, Komorbidität
- Therapiedaten (Substanz, Dosierung, Beginn und Ende, …)
- unerwünschte Ereignisse

▸ **Patient u.a.:**
- PROs: Schmerz, Funktion, Lebensqualität
- Arbeitssituation
- Inanspruchnahmeverhalten

Quelle: Prof. Dr. Zink

Abbildung 2: In festgelegten Abständen werden mindestens fünf, möglichst zehn Jahre lang vom Arzt der klinische Status, Details zur Therapie sowie unerwünschte Ereignisse dokumentiert.

range of indications, which investigates with high quality standards the safety and efficacy of new therapies against the backdrop of many influencing factors (e.g. comorbidity, comedication, therapy history, activity and severity of the disease, patient characteristics). A comprehensive inclusion of all patients in treatment would be neither feasible nor meaningful due to the large number of patients. We therefore work with spot samples from internist rheumatologists, whom consecutively include their patients newly starting biologics/biosimilar or csDMARD after previous therapy failures.

When we compare these spot samples to other large-scale rheumatological data collections in Germany, RABBIT can be considered representative of the target group of patients with at least one prior therapy failure. Even more important to the generalisability of the results is that – unlike in clinical trials – the inclusion of patients is not limited by any other exclusion criteria than the diagnosis and the

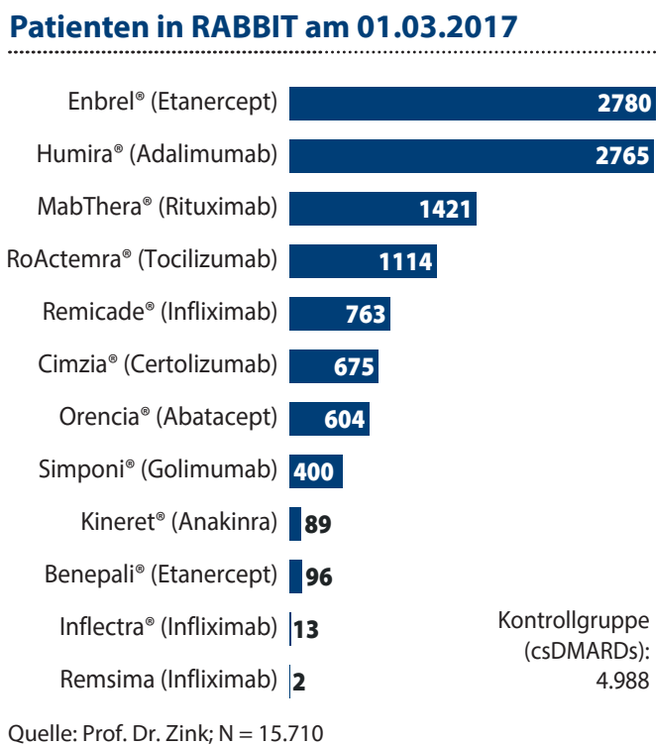


Abbildung 3: Inzwischen sind mehr als 15.700 Patienten in das Register aufgenommen worden.

commencement of an approved therapy.

RABBIT also allows the comparison of the efficacy of different substances when influencing factors such as patient characteristics and therapy sequence are used as control. In contrast to meta-analyses of clinical trials, in which the various new substances are compared to each other by means of a bridge comparator such as Methotrexate, a study like RABBIT has the advantage that all patients are monitored under the same conditions and that there is no heterogenicity with respect to the healthcare system or ethnic backgrounds.

1.3 Funding of RABBIT

RABBIT is not only innovative with respect to the observation of an entire class of drugs, but also as far as funding is concerned. All manufacturers of biologics or biosimilars which are approved for RA therapy in Germany participate in equal cost-sharing since they have obtained marketing authorisation for the respective substances. At this time there are eight, expected soon to be twelve different manufacturers. They have committed to lend very long-term support (> 10 years).

A uniform contract regulating the cooperation has been signed by all manufacturers and the DRFZ (and also the Academy for Advanced Rheumatologic Training as disbursement service provider to facilitate compensation payouts to documenting practitioners). The study administration of the DRFZ has retained full academic autonomy in the maintenance of the registry and in the publication of results. The pharmaceutical companies are provided with semi-annual reports on severe adverse events which have occurred with their substance or in the control groups.

They furthermore receive comprehensive interim reports regarding their substances in ten-year-intervals, which include comparisons to the control group and the other substances in which adjustments are made to account for the different risks within the individual therapy groups. The pharmaceutical companies forward their semi-annual and interim reports to the European Medicines Agency EMA in the course of their risk management plans.

1.4 Legal classification of RABBIT

Every now and then the question is raised whether registries like RABBIT are subject to the German Medicines Act (AMG) as non-interventional studies (NIS) subject to reporting requirements, because they receive funding from pharmaceutical product manufacturers. We (together with

our colleagues abroad and representatives of the AMA) firmly hold the opinion that observational studies of this type cannot be subject to the AMG. The regulations of the AMG applicable to NIS are intended to prevent marketing-motivated abuses by demanding that the study-conducting pharmaceutical company as well as all participating physicians report all received payments to the National Association of Statutory Health Insurance Carriers. This provides a meaningful means of control as to whether the participation in an NIS constitutes an incentive to prescribe certain drugs.

In the case of RABBIT, there are no incentives whatsoever to prescribe any specific therapy, since patients receiving new prescriptions for any approved therapy, including conventional drugs, can be included. A reporting requirement similar to the AMG would increase the administrative burden to an extent that would exceed the capacities of an independently operated registry.

2. Results from RABBIT

2.1 Comparison to randomised clinical trials

Randomised clinical trials (RCTs) are the gold standard for evidence of the efficacy of therapies. Case numbers are calculated to provide this evidence. Aspects of therapy safety can only be investigated for very common and short-term events. Correspondingly, each therapy arm requires at least 600 patients to prove a risk increase from four to eight events per 100 patient-years. Such case numbers are hardly ever met by randomised studies. It is even much more difficult to identify risk increases of rare but important events with an incidence rate of less than one per 100 patient-years.

Methodical and ethical reasons necessitate that randomised clinical trials stipulate many exclusion criteria. Accordingly, pregnant women, patients with prior cancers, old patients or patients with severe concomitant diseases are not accepted in RCTs in the vast majority of cases. The high internal validity of RCTs – where patients of different therapy arms are entirely comparable due to randomisation – is juxtaposed to the low external validity. The included patients are not representative of the patients to be treated with the substance later on. When we compare RABBIT patients to those patients used to test the drug in the course of the approval study, we find that less than one third of those patients treated in applied routine healthcare would have met the inclusion criteria of the clinical trial [1]. The patients treated in practice are older, often female, have more comorbidities and more severe functional limitations. This affects the efficacy as well as the safety of the drugs. Correspondingly, we find in patients that meet the inclusion criteria of the respective approval studies much less severe infections than in those that do not meet the criteria. An extrapolation of the infection risk from randomised clinical trials thus inevitably leads to an underestimation. The compatibility of the results from clinical trials is therefore limited. The primary domain of registries is not the efficacy but the safety of therapies. Here, they provide a substantial contribution to risk evaluations.

2.2 Results regarding therapy safety

With respect to the original questions – infection-, malignoma- and mortality risks – we now have very solid data available. Additional questions refer to specific risk groups or risk constellations, including with regard to comedications. Here, a lot of work remains to be done. The following shall summarise the so-far most important results regarding therapy safety.

2.2.1 Cancer risk of biologics therapy

With respect to newly occurring cancers, neither RABBIT

nor other European registries have found a general risk increase of biologics compared to conventional therapies. Newer studies suggest that RA must lead one to assume a higher general risk of melanoma [2, 3]. Based on observations made by the Swedish biologics registry [4] that found a 50-percent increase in the risk of a malignant melanoma during biologics therapies compared to conventional therapy, the data of eleven European registries comprising of almost 600,000 patient-years in observation time was jointly analysed. However, in summary no indication of an increased risk caused by biologics therapies was found [5].

It is known that RA is associated with an increased lymphoma risk, especially in the presence of persistently high disease activity [6]. None of the European registries has observed and increased lymphoma risk in biologics therapies. To additionally investigate whether there are sub-type shifts (B-cell-T-cell-lymphoma, etc.), the data of eleven European registries was jointly analysed. The comforting result was that none of the subtypes showed any deviation whatsoever from the expected values in the general population [7]. One should rather expect that improved control of disease activity will reduce the lymphoma risk in RA in the long run.

Neither the German nor the British biologics registry have observed an increased risk of recurrence of a malignant disease under TNF-inhibition when the patient history included prior malignoma [8, 9]. Most recently patients with malignoma in the patient history are primarily treated with Rituximab, which is known from lymphoma therapy. All results obtained so far suggest that this will lead to a recurrence risk comparable to the therapy standard [10].

2.2.2 Risk of cardiovascular disease

The data of RABBIT prove that extended and persistent high inflammatory action constitutes a significant risk factor for the development of secondary complications [11, 12]. In our current investigations we were able to demonstrate this for the most important cardio- and cerebrovascular events, myocardial infarction and stroke.

Patients with heart failure also benefit from a consistent reduction of inflammatory action. The contraindication heart failure listed on some biologics labels was thus not supported by RABBIT data. Much rather, heart failure patients (NYHA grades 1-3) with high and uncontrolled disease activity showed a five-fold increased risk of getting severe infections or to die of them. The data strongly suggest that successful biologics therapy can reduce the risk of severe fatal infections even in risk patients (e.g. those with heart failure) [13].

2.2.3 Risk of severe infections

Various registries have consistently shown that the risk of severe infections under biologics is elevated compared to conventional therapies [14, 15], and that this elevation is particularly pronounced during the first three to six months of the biologics therapy [16, 17]. On one hand, this demonstrates a general methodical problem of longitudinal studies: patients with a high risk of severe infections are more often excluded from the biologics group of the therapy cohort, either because they are switched to conventional disease-modifying therapy (csDMARDs) after an infection, or due to aborting the therapy due to other risk factors or because they expire. The longer the observation continues, the more patients with lower risk remain in the cohort.

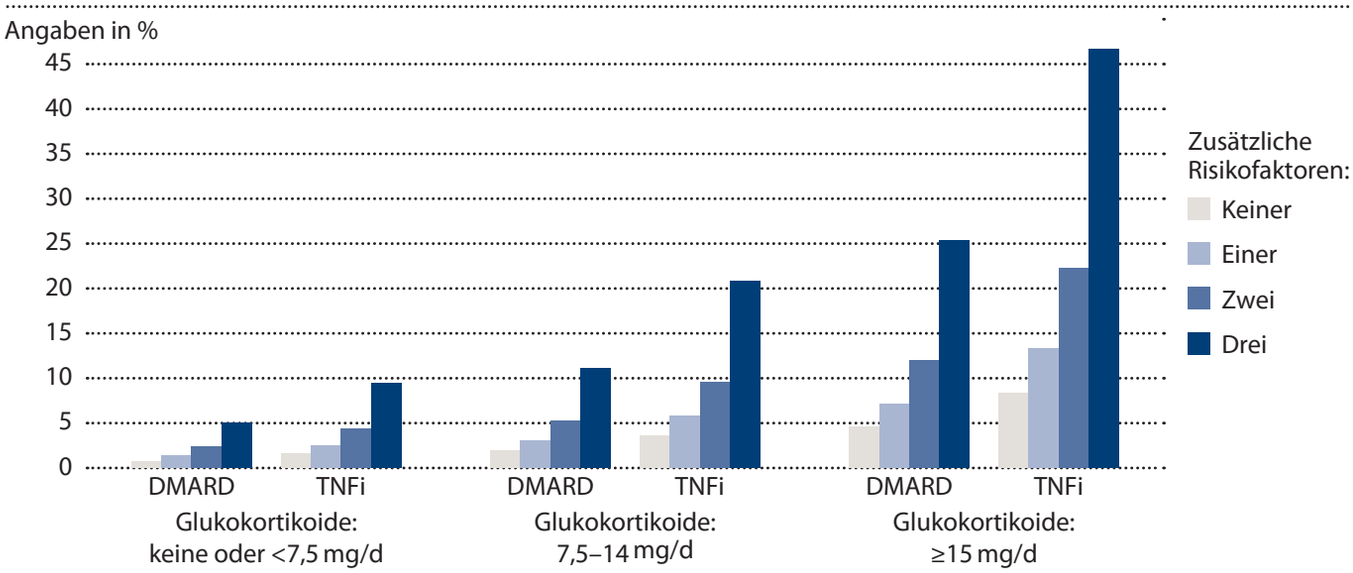
On the other hand, the specific risk of individual patients changes over time due to changes in the disease activity, the ability to function, the dosage of concomitantly administered glucocorticoids or due to the occurrence of new concomitant comorbidities. Regardless of the specific ob-

servation period, RABBIT shows a risk increase for severe infections under biologics by a factor of 1.8 [17, 18].

This risk must be viewed in the context of competing risks: high disease activity combined with a high dosage of concomitantly administered glucocorticoids contribute to an increased risk of infection. An effective therapy managing to reduce disease activity, lower the glucocorticoid dosage and improve the patient's physical ability to function is linked to an overall reduction of the infection risk [17, 18]. Thus, the risk must be weighed and balanced. Figure 4 illustrates the link between therapy with csDMARDs or biologics with various dosages of glucocorticoids and the risk factors of patients (advanced age, comorbidity, prior therapy attempts, prior infections). The RABBIT risk score for severe infections calculates the risk under various therapies to suffer a severe infection within the next twelve months. An online risk score calculator is available at www.biologika-registry.de (see Figure 5).

RABBIT has shown that the risk of herpes zoster especially during treatment with monoclonal antibodies against TNF is higher than that associated with csDMARDs, while no risk increase was found for the fusion protein [19]. This difference between different TNF-inhibitors agrees with observations made in tuberculosis [20, 21].

Ein-Jahres-Risiko für schwerwiegende Infektionen nach Therapie und Risikoprofil



DMARD: Disease-modifying anti-rheumatic drug; TNFi: Tumornekrosenfaktorhibitor
Quelle: Strangfeld A et al. Ann Rheum Dis 2011;70(11):1914–20

Abbildung 4: Zusammenhang zwischen Therapie mit csDMARDs oder Biologika, Begleittherapie mit unterschiedlichen Dosierungen von Glukokortikoiden und Risikofaktoren des Patienten. Risikofaktoren sind: Alter >60 Jahre, schlechte körperliche Funktion, chronische Lungen- oder Nierenerkrankung, anamnestische Infektion, mehrere Therapieversagen.

More than 30 years ago it has already been observed in animal testing that an immunisation with TNFalpha can prevent sepsis in artificially created infections. Subsequent trials regarding the treatment of patients with already existing sepsis with TNFalpha inhibitors were unsuccessful. We have now demonstrated that the risk of contracting sepsis following a severe infection or to die due to the infection is substantially reduced in patients receiving biologics at the time of the infection compared to those patients that have not been treated with biologics [22]. Thus, the registry has, for the first time, confirmed animal testing results. The results raise the question if, for example, the therapy should generally be discontinued before planned surgery. This clinically very relevant problem should be investigated in a randomised clinical trial.

2.2.4 Rare events

In the approval study for Tocilizumab, an IL-6 antibody, an increased incidence rate of perforations in the lower gastrointestinal tract was observed. A risk analysis was not possible as there were no results in the control group. Registries such as RABBIT can comparatively analyse such safety indicators. We have found a 4- to 10-fold increased risk compared to other therapies [23]. The mechanism of action inhibits the generation of the C-reactive protein, which can lead practitioners who are not familiar with the therapy underestimate the importance of the problem. In such a scenario, registries can contribute to raising awareness among practitioners and patients in order to prevent severe progressions of this rare but grave complication.

2.2.5 Mortality risk under biologics therapy

It has long been known that rheumatoid arthritis is linked to increased mortality [24-27]. In RABBIT, a standardised mortality rate of 1.5 was found in the German standard population [28]. This corresponds to what one would expect in RA [29]. A persistently increased disease activity was a strong predictor of premature mortality. The risk of death in patients with persistent high disease activity was three times that of the standard population, while risk the in patients with low to moderate cumulative disease activity was not different from that of the age-appropriate standard population.

Figure 6 shows the five-year survival rate for women and men ages 50 or 65 with a combination of the risk factors smoking and comorbidities. In persistent high disease acti-

Berechnung des Risikoscores

60 Jahre oder älter	◉ ja ○ nein
Wert für Funktionskapazität FFbH (zwischen 0–100)	Score bekannt… ▼ FFbH-Wert: 68
Schwerwiegende Infektion (letzte 12 Monate)	○ ja ◉ nein
COPD oder andere chronische Lungenerkrankung	◉ ja ○ nein
Chronische Nierenerkrankung:	○ ja ◉ nein
Anzahl abgesetzter DMARDs/Biologika:	◉ <5 ○ ≥5
Behandlung: Glukokortikoide (im Mittel in Prädnisolonäquivalenz/d):	○ <7,5mg ◉ 7,5–15mg ○ >15mg
	○ TNF-Blocker ○ Abatacept ○ Rituximab ○ Tocilizumab ◉ nur synthetische DMARDs

Die Wahrscheinlichkeit, innerhalb der nächsten 12 Monate an einer schwerwiegenden Infektion zu erkranken, beträgt 4,7 %

Quelle: www.biologika-register.de

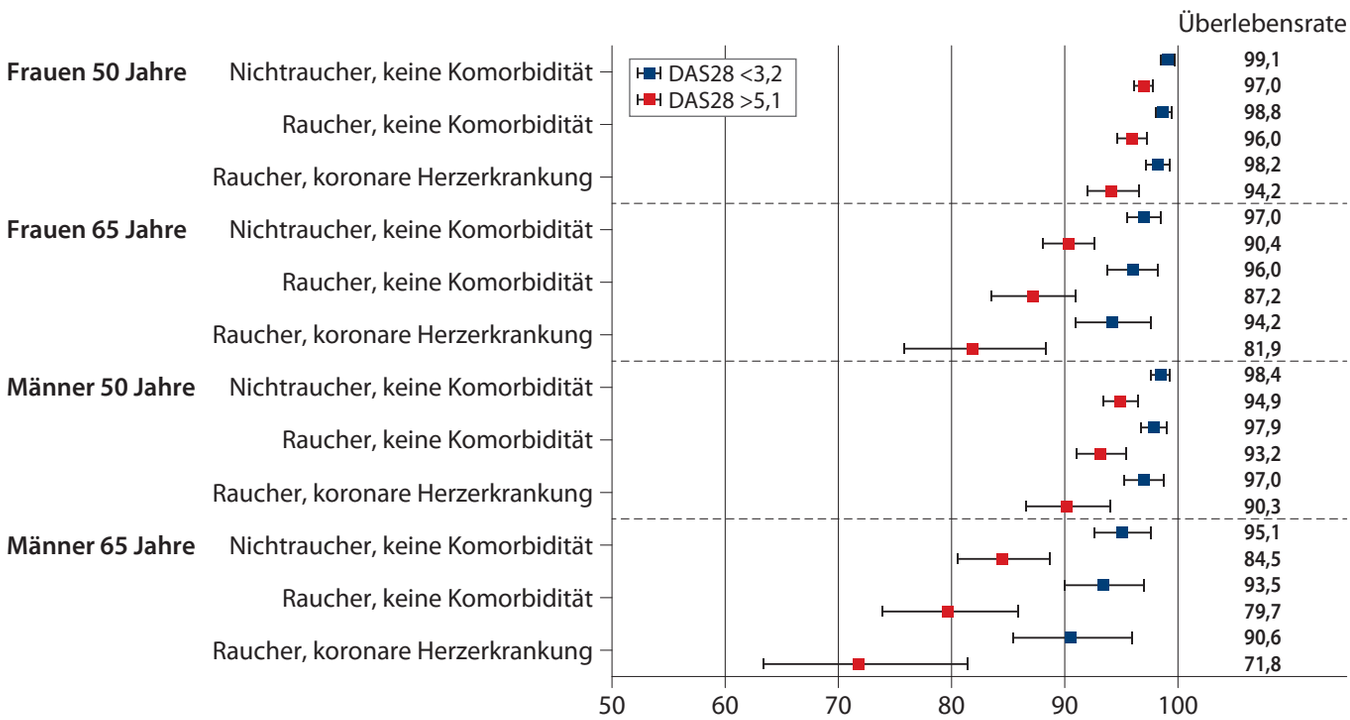
Abbildung 5: Der RABBIT Risiko-Score errechnet das Risiko, binnen eines Jahres an einer Infektion zu erkranken.

vities, the survival probability is reduced by up to ten years. Patients treated with TNF-inhibitors or Rituximab had a significantly lower mortality risk than patients that were not treated with biologics but with csDMARDs instead (reference group: Methotrexate) (see Figure 7). Biologics were still superior even when the reduction of disease activity was included in the calculation, meaning, when patients were compared whom had achieved the same level of disease activity in therapies with synthetic or biological DMARDs.

3. Summary and conclusion

As mentioned before, the applied healthcare reality of patients treated with approved substances systematically deviated from patients included in RCTs. In this scenario, long-term observational studies such as RABBIT are of gre-

Fünf-Jahres-Überlebensraten von Patienten mit DAS28 <3.2 oder DAS28 >5.1 in mehr als 80 Prozent der Beobachtungszeit



Quelle: Listing J et al., Ann Rheum Dis 2015 Feb; 74(2):415–21

Abbildung 6: Überlebenswahrscheinlichkeit bei hoher oder niedriger Krankheitsaktivität in Kombination mit Rauchen und Begleiterkrankungen.

at importance to the assessment which patient group benefits particularly well from which therapy, and which at times rare risks which can only be identified with large case numbers affect certain subgroups.

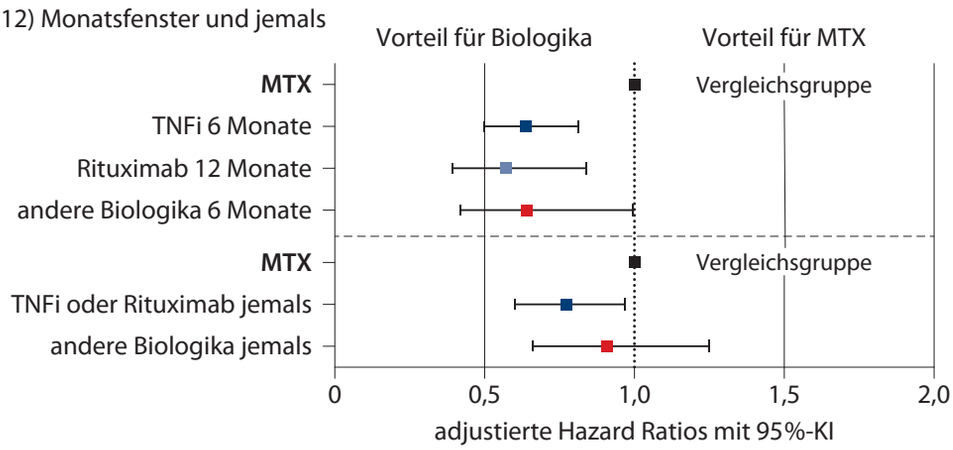
For this reason, independent observational studies should always be conducted when innovative new drugs obtain marketing authorisation. We deem it appropriate that the pharmaceutical companies should take on this responsibility in the same manner as it is done RABBIT. Legal regulations intended to secure full academic autonomy of the registry have comprehensively and successfully been tested by the example of RABBIT.

RABBIT has successfully demonstrated the great importance of permanent disease activity control in the prevention of secondary complications. The infection risks can be assessed in the context of other patient-specific risks. We have also demonstrated that registries can generate proper hypotheses which should then be confirmed in randomised clinical trials. With an ever-increasing number of different substances, it will remain necessary to monitor how long-term therapies with many therapy changes affect disease progressions and the risks of undesired effects. In this regard, it is a long way to all remaining questions being answered.

A registry like RABBIT is not limited to drug surveillance. It is a disease registry which becomes more valuable the longer it is maintained. Thus, ways should be created to obtain permanent funding for successful registries. Crucial factors are a long term perspective, quality assurance and proven methodological expertise, in order to ensure that high-quality registries are being supported.

Zusammenhang zwischen Biologikabehandlung und Mortalität (Methotrexat als Goldstandard)

6 (12) Monatsfenster und jemals



	Pat.-Jahre	Adj. HR
MTX	**7.012**	**Vergl.-gr.**
TNFi 6 Monate	16.843	0,64
Rituximab 12 Monate	2.599	0,57
andere Biologika 6 Monate	1.654	0,64
MTX	**6.469**	**Vergl.-gr.**
TNFi oder Rituximab jemals	22.370	0,77
andere Biologika jemals	2.809	0,91

Hazard Ratios adjustiert für allg. Risikofaktoren, DAS28, Glukokortikoiddosis, Funktionsfähigkeit
Quelle: Listing J et al., Ann Rheum Dis 2015; 74:415–21

Abbildung 7: Mit Biologika behandelte Patienten haben ein geringeres Mortalitätsrisiko als in der Vergleichsgruppe.

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Evidence Gaps in Benefit Assessment – what does Registry Data offer?

Dr. Norbert Marschner, Dr. Martina Jänicke | Clinical Research Centre iOMEDICO, Fribourg

In healthcare, cancer diseases are a central area of concern due to their high incidence rates and mortality. To date, approximately one third of all benefit assessments are conducted for oncology drugs. Data from clinical tumour registries today already support benefit assessments in the definition of the comparator therapy as well as in the estimation of the target patient population. Methodologically sound and analysed prospective registry data could furthermore be used in the evaluation of patient-relevant endpoints and deliver information on the efficacy of new drugs compared to the standard therapy when marketing authorisations were granted on the basis of single-arm studies.

With approx. 500,000 new cancer diagnoses annually, cancerous diseases constitute a central challenge to the healthcare system. As they more often occur in people of advanced age, the demographic change of society suggest that an increase of cancerous diseases is to be expected in the future. Due to the tremendous advances in oncology research in recent decades, approximately half of all cancerous diseases are now curable. This puts into the spotlight long term side effects and other late effects such as ability to work and early pensions, as they burden the respective social systems substantially.

The term cancer describes a category comprised of a multitude of different diseases with differing incidence rates, treatment courses and prognoses. For example, the approximately 70,000 annual new breast cancer diagnoses are juxtaposed to a mere 2,000 new diagnoses of Morbus Hodgkin. While the five-year survival rate after a testicular cancer is now 95 percent, less than ten percent of patients with pancreatic tumours (pancreatic cancer) are still alive in the fifth year after the diagnosis [1]. Depending on the cancer diagnosis and the stage of the disease, the therapy priority can either be to cure the disease, meaning the reduction of the risk of recurrence while simultaneously preventing long-term side-effects, or, alternatively the management of symptoms, quality-of-life maintenance and the possible extension of the survival time.

The discussion of pitfalls and evidence gaps in the benefit assessment of oncological drugs should take into consideration the specific peculiarities of the respective disease: the question of the added benefit for a cancerous disease with a more chronic multi-year progression and multiple well-compatible treatment options must be answered differently than for a cancerous disease with unfavourable

prognoses and only view approved drugs available.

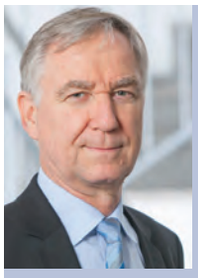
Benefit assessment in oncology

Oncological research is a very dynamic field, which is reflected by the high number of clinical trials underway in which new drugs are being tested. Approximately one third of all benefit assessment undertaken since the introduction of the AMNOG law concerned oncology drugs. [2]

Due to the at times high mortality rates and very short survival times there is tremendous pressure to quickly approve new and potentially efficient drugs. Correspondingly, US and European approval authorities, namely the FDA and the EMA, have created accelerated assessment procedures which allow early accelerated/conditional approvals, provided that surrogate- or preliminary endpoints suggest that a drug might have patient-relevant benefits. This development poses a new challenge to the benefit assessment procedure introduced with the AMNOG law. Drugs are being approved that have met the approval requirements (proof of efficacy), but cannot or not yet meet the requirements of the benefit assessment (proof of better efficacy than the standard). This can occasionally cause the pharmaceutical companies, IQWIG/G-BA and medical societies to come to differing conclusions where the benefit assessment of a new oncological drug is concerned. This therefore poses the question whether additional data, e.g. from clinical tumour registries, can support these discussions and close evidence gaps.

Clinical tumour registry

Clinical tumour registries, also known as cancer registries, are cohort studies in which patients with certain cancer diagnoses (diagnosis-specific registry) or from certain residential areas (population-specific registries) can participa-



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Beispiele für prospektive, klinische Tumorregister

	Start	Referenz
Bevölkerungsbezogene prospektive, klinische Register		
Gemeinsames Krebsregister der neuen Bundesländer	1952	(3,4)
Tumorregister München	1978	(5)
Nationales Krebsregister	Im Aufbau	(6)
Diagnosespezifische prospektive, klinische Register		
Tumorregister Kolorektales Karzinom	2006	(1)
Tumorregister Mammakarzinom	2007	(7)
Tumorregister Nierenzellkarzinom	2008	(8)
Tumorregister Lymphatische Neoplasien und Multiples Myelom	2009	(9,10)
Tumorregister Lungenkarzinom	2010	(11)
Tumorregister Pankreaskarzinom	2013	(12)
CRISP (Nicht-kleinzelliges Lungenkarzinom, AIO-TRK-0315)	2015	(13)

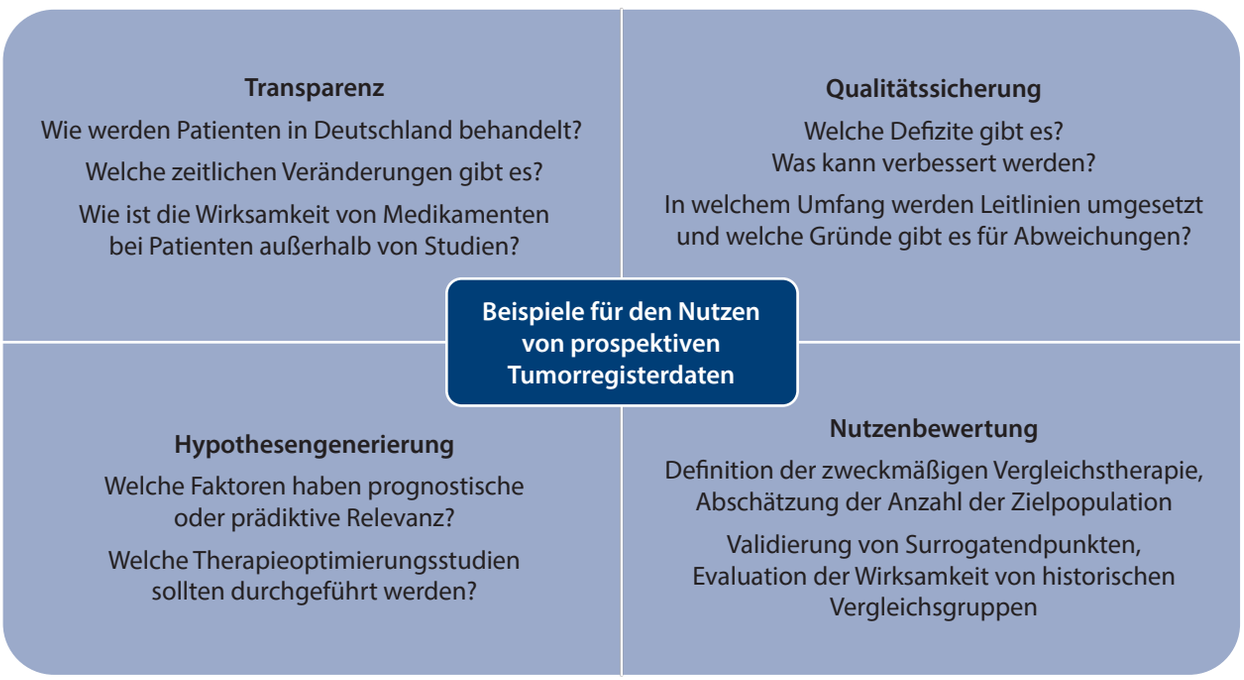
Quelle: Dr. Jänicke

Tabelle 1: In klinischen Tumorregistern werden, anders als in rein epidemiologischen Registern, alle Daten zur Behandlung und zum Verlauf der Erkrankung dokumentiert.

te (see Table 1). In contrast to solely epidemiological registries which only collect diagnoses, demographic data (age and gender) as well as the date of death, clinical registries record all data concerning the treatment and the progression of the disease. Population-specific registries collect uniform basic data on all cancerous diseases, whereas diagnosis-specific registries are focused on the comprehensive collection of specific details of individual cancerous diseases.

The data generated in clinical tumour registries can be generally useful to many questions and topics in research and the healthcare system in general. They primarily create transparency in in the realities of treatment and can be used for quality assurance and hypothesis generation as well as to support the benefit assessment (see Figure 1). Insights into applied treatment generate not only essential transparency in our healthcare, but also facilitate the observation of diagnostic and therapy changes over time

Beispiele für den Nutzen von prospektiv erfassten Tumorregisterdaten



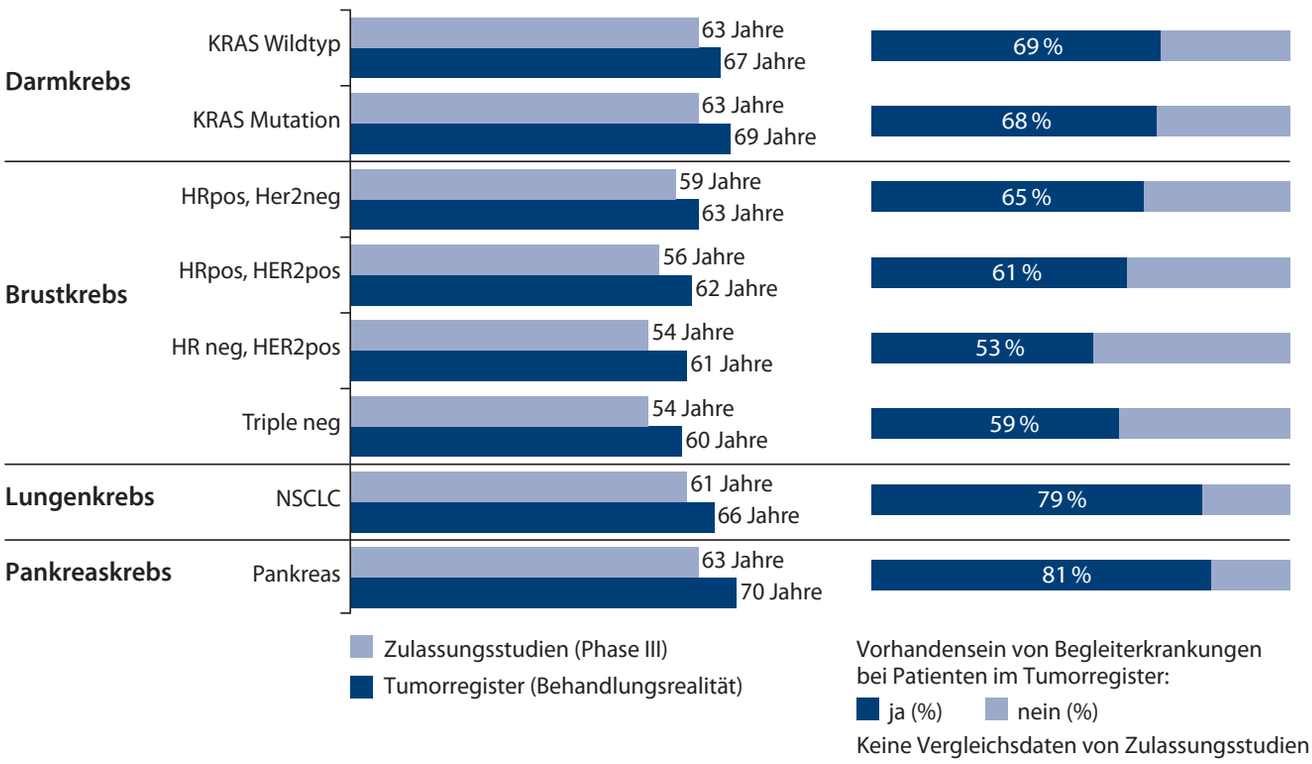
Quelle: Dr. Jänicke

Abbildung 1: Daten aus klinischen Tumorregistern können für unterschiedliche Zwecke genutzt werden, unter anderem zur Qualitätssicherung oder zur Unterstützung bei der frühen Nutzenbewertung.

along with the analysis of drugs outside of clinical trials. The last point is important because patients who are permitted into clinical trials are usually different from the totality of all treated patients in Germany because of the stringent inclusion- and exclusion criteria of clinical trials. Thus, patients participating in approval studies are often younger and have less comorbidities than patients that cannot or are not allowed to participate in studies (see Figure 2). This fact can be reflected in survival rates (see Figure 3). [8]

Data from clinical tumour registries make it possible to investigate which areas of treatment can be improved, e.g. by analysing how many patients are being and can be treated in compliance with recommendations/guidelines, what the reasons for deviations are and where recommendations should be reviewed or where treatment must be improved. And lastly, explorative analyses facilitate the identification of relevant prognostic factors and the formulation of hypotheses on the efficacy of treatments compa-

Medianes Alter bei Therapiebeginn und Häufigkeit von Begleiterkrankungen bei Patienten mit Stadium IV-Krebsdiagnosen



Quelle: Daten basierend auf einer Analyse der klinischen Tumorregister Kolonkarzinom, Mammakarzinom, Lungenkarzinom und Pankreaskarzinom, N=4.865

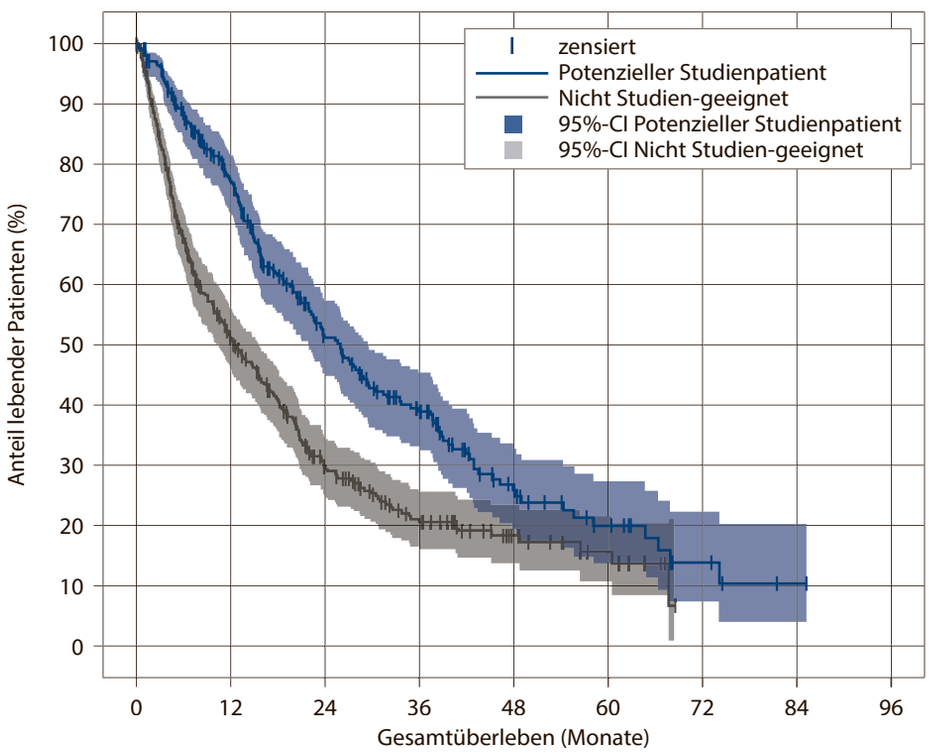
Abbildung 2: Angesichts der Ein- und Ausschlusskriterien sind die Patienten in Zulassungsstudien häufig jünger als die Gesamtheit des Patientenkollektivs und haben weniger Begleiterkrankungen.

red to each other. The latter should subsequently be tested with randomised clinical trials.

Data of clinical cancer registries in Module 3 of the benefit assessment: appropriate comparator therapy, number of patients in the target population

In Module 3 of the dossier for the benefit assessment, the pharmaceutical company provides data of the appropriate comparator therapy as well as on the number of patients in the target population. This data is then used to estimate the costs to the SHI. Discussions with the G-BA regarding the definition of the comparator therapy ideally commence as early as during the design phase of the ap-

Unterschiede im Gesamtüberleben zwischen potenziell Studien-geeigneten und nicht-Studien-geeigneten Patienten mit metastasiertem Nierenzellkarzinom



Patients at risk									
Potenzieller Studienpatient	313	203	107	69	28	14	5	1	0
Nicht Studien-geeignet	419	179	81	42	18	8	0		

Quelle: übersetzt und modifiziert aus Marschner et al., 2017 (8) mit freundlicher Genehmigung von Elsevier

Abbildung 3: Unterschiede zwischen potenziell für Zulassungsstudien geeigneten und nicht-geeigneten Patienten spiegeln sich auch in Daten zum Gesamtüberleben wider.

proval study, but no later than before the dossier is created. Approval criteria and guidelines are usually used as the source of the definition of the appropriate comparator therapy.

This gives rise to two types of problems: on one hand, the creation of well-researched guidelines takes time, and particularly in highly dynamic indications such as in oncology these guidelines can already be outdated at the time of the evaluation. On the other hand, it is possible that in practical application patient characteristics such as comor-

bidities more often than expected strongly relativize the standard recommendations of the guideline, thus necessitating that other therapies are selected. The appropriate comparator therapy defined on the basis of the guidelines will not correspond to real-life treatment standards in both scenarios.

Prospective clinical tumour registries can solve this conflict, as they provide representative insights into the actual treatment reality, thereby facilitating the definition of the appropriate comparator therapy based on the treatment standard in Germany at the time a study commences.

Clinical tumour registry data in Module 4 – benefits and added benefits

In Module 4 of the dossier for the benefit assessment the pharmaceutical company provides data regarding the added benefit of the new drug. This should be done on the basis of randomised controlled clinical trials and patient-relevant endpoints. Since the introduction of the benefit assessment pursuant to the AMNOG law, two particular topics have kept the oncology field occupied: the handling of early benefit assessment approvals based on single-arm (Phase II) studies and the patient-relevance of the progression-free survival.

Due to the rarity of spontaneous remissions in cancerous diseases, a tumour responding to a new drug in a single-arm study may very well be considered proof of efficacy and thus benefit from the perspective of a physician. In the opinion of many medical societies, every newly approved drug constitutes an addition to available treatment options, especially in consideration of patients with incompatibilities or comorbidities. However, from the methodical and healthcare-economic perspective of QWiG/G-BA, single-arm study data does not constitute proof of an added benefit (better efficacy than the therapy standard).

An additional later benefit assessment after randomised Phase-III data was submitted or obligating randomised Phase-IV-studies after approval could be discussed as possible solutions. At the same time, however, recruitment into randomised trials often becomes very difficult after early approvals, because patients and/or practitioners reject the randomised assignment of the treatment.

Currently, the utilisation of „historical controls", meaning data published about patients with identical or comparable indications, constitutes the only option to close the evidence gap in the early benefit assessment of drugs that were approved on the basis of single-arm studies. However, historical controls have limited statistical value for a multitude of reasons. Thus, differences between patient groups, study types and analysis methodology can suggest efficacy differences to healthcare systems that aren't really differences. Tumour registries are also not able to provide added benefit evidence with a high statistical reliability, because patients are not assigned randomly to the therapies but rather based on decision factors on the side of the practitioner and the patient, which can result in differing medical and demographic characteristics.

Properly designed and high-quality prospective registries with an adequate analysis methodology can, however, provide solid indications regarding the possibility of the new drug having better efficacy and/or better compatibility than the prior standard including after the approval. In contrast to the comparison with historical controls, such an approach has the decisive advantage that data is being collected in a uniform manner and that the patients were treated in the same period of time at the same facilities. In a subsequent second benefit assessment at a later time this data can then provide valuable indications regarding the added benefit available in the scenarios described above.

Einsatzbereiche von Tumorregisterdaten bei der Nutzenbewertung

Bei Zulassung / Frühe Nutzenbewertung	
Definition der zweckmäßigen Vergleichstherapie?	✔
Bewertung / Validierung von patientenrelevanten Endpunkten?	✔
Analyse der Wirksamkeit von Vergleichstherapien (historische Kontrolle) bei Vorliegen von einarmigen Studiendaten	?! mit adäquater Methodik
Nach Zulassung / Späte Nutzenbewertung	
Beurteilung der generellen Wirksamkeit (Nutzen)	?! mit adäquater Methodik
Hypothesengenerierung zur Wirksamkeit gegenüber Vergleichstherapien → Unterstützung der Studiendaten zum Zusatznutzen	?! mit adäquater Methodik
Bewertung der Wirksamkeit gegenüber Vergleichstherapien mit hoher statistischer Aussagekraft → Definitive Beurteilung des Zusatznutzen	✕

Quelle: Dr. Jänicke

Tabelle 2: Während Registerdaten schon heute in die frühe Nutzenbewertung einbezogen werden, könnten sie, bei Anwendung adäquater Methodik, auch zu späteren Zeitpunkten Evidenzlücken schließen.

The AMNOG law defines four types of „patient-relevant" endpoints for the benefit assessment: (i) extension of the survival time, (ii) the reduction of morbidity (caused by the symptoms caused by the disease), (iii) the reduction of undesired effects and (iv) quality-of-life improvement. For many cancerous diseases, the proof of efficacy and thus the approval are based on tumour response or the progression-free survival time (PFS). These endpoints can be met faster than obtaining overall survival rates, which can lead to a reduction of study durations and earlier approvals. However, the evidence for an added benefit pursuant to AMNOG criteria can hardly be established with this data. Convincing data establishing a correlation of these endpoints to overall survival has not yet been established. The requirements for the validation of surrogate endpoints are high – and justifiably so. At the same time, establishing such proof is made even more difficult by the fact that many studies allow the switch to new drug for ethical reasons if the disease keeps progressing.

There probably won't be a universal solution to this topic. Particularly the discussion of patient-relevance of the PFS should be entity-specific. Tumour registries are valuable data sources for the entity-specific validation of endpoints, especially when quality-of-life data is also being collected at the same time.

Quality standards of tumour registries

Tumour registry data is already being cited in Module 3 today. In the future, this data could also support the discussions in Module 4 or a late benefit assessment. In order to evaluate the quality and representativeness of the utilised data sources, a candid discussion of the standards for the design, conduct and analysis of registry data is sorely needed. Even seemingly simple surveys and analyses regarding the commonness of a given treatment are susceptible to biases when unsuitable collection- and analysis methods were chosen and when influencing confounders were not properly considered. At this time and especially in oncology, an amalgamation of supposedly prospective data which is actually retrospectively collected routine data introduces biases into survival analyses which are hardly identifiable to non-experts.

A faulty design of tumour registries or of specific analyses can lead to results which do not adequately reflect reality (example explained in reference 14). A lack of quality assurance controls in the execution can lead to incomplete and faulty databases, which can severely affect subsequent analyses. The comprehensive consideration of influence factors is essential to the interpretation of tumour registry data (example explained in reference 5). The quality assurance methods known from clinical trials are only partially applicable to registries.

Conclusion

Adequately designed, conducted and analysed clinical tumour registries can be a valuable data source which can complement the results of randomised clinical trials. In early benefit assessment, they can meaningfully support the discussion of the definition of the appropriate comparator therapy, the analysis of the patient collective and of the relevance of endpoints. In the future, prospective tumour registries could possible provide indications regarding the efficacy of newly approved drugs compared to the established therapy standard, and thereby complement single-arm study data regarding the added benefit.

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Registries have tremendous potentials, the permanent establishment is demanding

Dr. Florian Staeck

On March 10/11, the Interdisciplinary Platform on Benefit Assessment held its fifth conference under the general title „Handling Evidence Gaps in the Early Benefit Assessment" in Kelkheim. The Friday-afternoon lectures discussed legal, ethical and procedural aspects from the perspective of the Federal Joint Committee (G-BA) and the approval. On the second day, the discussion became more relaxed after two disease-related registries were introduced.

The latter offer valuable assistance in answering many questions not limited to pharmacovigilance. At the same time, they augment evidence with real world data, whose basis reflects the results of randomised clinical trials. It would also be a great benefit if the results of registries could be integrated into regulatory decision-making in a timely manner. This type of data would be highly interesting in the „late" benefit assessment. The establishment of new registries which are capable of generating high-quality data is methodically demanding. Furthermore, their establishment often fails due to a lack of permanently committed structures and a lack of long-term funding commitments. The participants of the Interdisciplinary Platform pointed out this fact in their conference.

The thorough taking of inventory of just what registries can and cannot offer constitutes an important contribution to breaking the deadlock in the debate between proponents of randomised clinical trials (RCT) on one side and the supporters of „real world data" on the other. Up until now, the two factions merely confront each other with what the respective other instrument cannot offer, noted the participants. The existing options for institutional support of registries have been described as insufficient. For example, there were reports of a lack of support for existing registries by the Federal Research Ministry. Even in the course of the EU initiative „Horizon 2020" subsidy applications failed to succeed, noted the participants.

State funding is controversial

There was a controversial debate in which form and by which actors support and funding should ideally be provided. This applies particularly in light of the fact that the costs of the German RA registry RABBIT, for example, are relatively manageable at merely 1.5 million Euros annually. This sum must be put in the context of the revenues generated from the SHI by biologicals – which amount to approximately two billion Euros annually. By itself alone this makes the case for appropriate sponsoring. Considering the 19 percent VAT surcharged on medicinal products, state funding of registries should be demanded. This was refuted with reference to prior experiences with state-financed registries. The cancer registry would demonstrate the pitfalls associated with the implementation of a registry within the confines of federal structure. It would remain a concern that the cancer registry would not provide the actually required data – despite extensive lead times and substantial taxpayer expenditures. A non-state solution e.g. in the form of self-administration would therefore be a better alternative.

However, doubts were also expressed about the sustainability of industry-sponsored registries. It would be only natural if the interest of a pharmaceutical company to fund registries were to diminish once patent protection has expired. Thus, the coupling of funding to the product cycle of a drug would not be sustainable.

The participants furthermore stressed the importance of the long term perspective of funding, which may well be the crucial factor overall. It was said that the common funding periods of three to five years will not go very far in the context of a meaningful registry.

A body of regulations for registries is indispensable

A body of regulations in which it would have to be specified how registries must be designed - preferably across all of Europe - was considered indispensable. The very heterogenous haemophilia registry of the EU was pointed out as an example for the consequences of a lack of harmonisation. It was stated that it is still highly controversial whether countries with conservative Factor VIII substitution application in mild haemophilia progressions have higher complication rates than countries like Germany, where traditionally high factor utilisation is rather costly.

With autonomy in mind, access to the data would have to be regulated in industry-sponsored registries and also in registries maintained at scientific institutions. It would be conceivable to make the evaluation of the data available to all participating healthcare systems in the form of scientific publications.

Many possible approaches to complementing RCT data with registry data were pointed during the platform conference. The data of the RA registry, for example, has confirmed that RCT provide high internal validity but at the expense of low external validity: Only 23 to 33 percent of the patients in the registry treated with biologics would meet the inclusion criteria of the approval study. Similar to tumour registries introduced at the platform conference: registries could support the definition of the appropriate comparator therapy or the evaluation of patient-relevant endpoints. Participants emphasised that the discussion of subgroups could also benefit from a review of registry data. Register data could also assist in determining whether the off-label-use of a drug could have patient-relevant advantages.

Approval authorities, it was said, were also increasingly confronted with evidence gaps. It was pointed out as a reminder that the German Medicines Act calls for severe reasons to withhold approvals. It would furthermore be impossible to interpret the Medicines Act to the effect that an active comparator would always be required in studies. This would in the case of evidence gaps often lead to conditional approvals, which would demand of the pharmaceutical company to submit new study data. However, in cases where data collected after the approval is not submitted – as is observed quite often –, a market retrieval of the preparation would de facto never be feasible, participants reported.

It would therefore be warranted to, on one hand, defend the demand for „good evidence“ in the approval proceedings. On the other hand, one would have to consult external data – including with the intent to quantify uncertainties from prior approvals. Here, the US would be years ahead of the EU. For example, the US approval authority FDA would have access to the Sentinel database. There, 223 million patient records are already available it was said. The „Sentinel Distributed Database“, which was established by the US congress in 2007, collects and processes data from 18 partner institutions and already provides observations spanning 425 million patient years. The United Kingdom and Scandinavia were also supposed to be far ahead of Germany in this regard. There, databases can assist in answering epidemiological question. In Germany, on the other hand, the debate has for years kept oscillating between the goal posts „data treasure“ and „data protection“ – and there is no end in sight.

The platform conference participants hotly debated boundaries and opportunities in the closing of evidence gaps in the case of orphan drugs. For these drugs, the legislature assumes the added benefit to be a given. It was also pointed out that in the 49 prior AMNOG proceedings for orphan drugs, the Federal Joint Committee was not able to quantify the added benefit in 34 cases. The argu-

ments made asserting that conducting RCTs would not be possible were often not convincing. It was said that only three proceedings had studies which included less than 50 participants. It was reported that the highest number of patients in a manufacturer dossier was 929, which made the term „rare disease" only partially applicable.

Increased uncertainty despite adjustments

In other cases, pharmaceutical companies had only submitted non-controlled single-armed studies or retrospective case series. This had given rise to differences between the study- and patient characteristics – i.e. with respect to prior therapies or collection times – which could not have been remedied by making adjustments. It was criticised that despite these adjustment procedures an increased uncertainty would have to be expected when consulting external control data such as from registries or observational studies. In these cases, orphan drugs had only had their added benefit confirmed on the basis of the legally required added benefit assumption.

This was countered with the statement that it was the political will of the legislature to promote orphan drugs. One would also have to consider the influence exerted by oftentimes well-organized patient associations. This it was alleged had made it impossible in some cases to recruit patients as study participants for RCTs because the patient associations had rejected them. Much rather, the approval authority had faced stiff opposition when stipulating registry conditions or practitioner training. It was then accused that would unnecessarily increase the costs of approval by setting the bar to high, it was said.

Orphan drug controversy

Furthermore, referenced were the four cases in which orphan drugs had to go through the entire benefit assessment procedure after the fact, because the prescription volume breached the threshold of 50 million Euros charged to the SHI. All these cases had confirmed that the positive added benefit reservations of the legislature were indeed justified. This sent a „strong signal" to orphan drugs, it was said. The other side commented that these cases simply revealed the impossibility to retroactively withdraw the prescription approval for drugs that had already been introduced to the market. This was in turn countered by the assertion that such assumptions which questioned the integrity of the proceedings for early benefit assessment were baseless.

With critical interest the peculiarities of this market segment were acknowledged, namely, the fact that after the approval of a substance used for a series of very rare congenital diseases no systemic follow-up investigation of long-term effects would occur. Participants complained about the practice of the European Medicines Agency EMA to remove orphan drugs from the database after ten years. This, according to the allegations, would unnecessarily complicate the tracking of the prescription volume.

The observation that manufacturers do not utilise the option to ask for the cost-benefit-analysis provided by the legislature was met with varying conclusions. This, it was said, could have been an option in the 30 cases in which manufacturers have withdrawn products from the German market. This argument was countered to the effect that even in the presence of a cost-benefit-analysis, the medical benefit would still remain the central factor pursuant to the respective ordinance. Furthermore, the efficiency threshold methodology applied by the IQWiG was deemed to be „arbitrary", in that the institute had disregarded the recommendations of healthcare economists. Against this backdrop and considering the long time required by this procedure, the instrument was called a „dead horse". The

fact that the National Association of Statutory Health Insurers had not ordered a cost-benefit-analysis since 2011 confirmed this assumption.

New uncertainty due to Higher Social Court decree

It was said the AMNOG proceedings had overall proven to be sustainable over recent years, because all that remained at the end of the proceedings were pure price negotiations. However, due to the decree issued by the Higher Social Court (HSC) Berlin-Brandenburg in the Albiglutid case, the availability of new drugs would be represented on the agenda more often than previously.

In defence and recovery proceedings, the judges have in March 2017 declared the prior practice of creating mixed pricing to be illegal. In this case an arbitration board had created the reimbursement amount as mixed price consisting of subgroups with and without determined added benefit. Previously, mixed prices were a strategic negotiation tool that allowed manufacturers to remain on the German market even when the G-BA had only asigned partial added benefits. This were to apply particularly when the appropriate comparator therapy pricing was considered acceptable by the manufacturer.

Paradigm change in the negotiation procedure?

The participants warned that the HSG decree might cause a paradigm change in the negotiation procedure. The conclusion would be that the judges' ruling would necessitate a higher reimbursement amount in groups with proven added benefits. This would then require monitoring to ensure that practitioners only describe the drug in these subgroups. In three out of four cases, however, the sick funds were not able to monitor in which subgroups prescriptions occur. It was then warned that a „prohibition" of mixed prices could in fact make procurement more expensive.

The legal position of the pharmaceutical company in the event of disputes regarding the added benefit is not very strong. The company would only be entitled to voluntrily participate in the German healthcare system. This applies similarly to the insured. Here, the withholding of a needed service or measure must not be arbitrary. It was said that the situation is different in the special case of the „Nikolaus"-ruling of the Federal Constitutional Court from 06 December 2005.

In emergency situations such as life-threatening disease and when all standard therapies have been exhausted as applies to this ruling, the required evidence standards establishing an obligation of the health insurance carrier to pay could be lowered. In 2013, the Federal Constitutional Court has explicitly reaffirmed that a claim by an insured which is based on the „Nikolaus"-ruling is confirmed independently of the actual costs. Accordingly, the ruling in this case stipulates that the obligation to assume costs of the health insurer must cover „the required amount".

One demand voiced by the participants was that regardless of a need to reform the AMNOG mechanisms for benefit assessments or the price determination process, political normative questions should not be hidden behind methodological debates.

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Evidence Gaps – what does Registry Data offer?

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